CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208434Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 208434 SUPPL # N/A HFD # N/A

Trade Name Alecensa

Generic Name alectinib

Applicant Name Hoffmann-La Roche, Inc.

Approval Date, If Known December 11, 2015 (expected)

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(1)

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

YES ☒ NO ☐

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

N/A

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

N/A

c) Did the applicant request exclusivity?

YES ☒ NO ☐

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

The product was granted orphan drug designation – 7 years exclusivity.

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

YES ☐ NO ☒

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

N/A

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

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

YES ☐ NO ☒

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

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

1. Single active ingredient product.

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

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference

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

YES ☐ NO ☐

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☐

If yes, explain:

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

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

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

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

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

Investigation #1

IND # YES ☐ NO ☐
Explain:

Investigation #2

IND # YES ☐ NO ☐
Explain:

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

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

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

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

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Gina M. Davis
Title: Senior Regulatory Health Project Manager
Date: December 10, 2015

Name of Office/Division Director signing form:
Title:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

GINA M DAVIS
12/11/2015

PATRICIA KEEGAN
12/12/2015

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: NDA 208434 Supplement Number: 0 NDA Supplement Type (e.g. SE5): _____

Division Name:DOP 2 PDUFA Goal Date: 03/03/16 Stamp Date: 7/6/2015

Proprietary Name: Alecensa

Established/Generic Name: alectinib

Dosage Form: Capsule

Applicant/Sponsor: Hoffmann-La Roche

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

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

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

Indication: Treatment of patients with ALK-positive. Locally advanced or metaastatic NSCLC who have progressed on or are intolerant to crizotinib.

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

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☒ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☒ indication(s); ☒ dosage form; ☒ dosing regimen; or ☒ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

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

Q3: Does this indication have orphan designation?

☒ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

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

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

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

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

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

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed$^{\Delta}$
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

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

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

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

Not feasible:

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

* Not meaningful therapeutic benefit:

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

† Ineffective or unsafe:

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

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

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

Δ Formulation failed:

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

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

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

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

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification** †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

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

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

* Other Reason: _____

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

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

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

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

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

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

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

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

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

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

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

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

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

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

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

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

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

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

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

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

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

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

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

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

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

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

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

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

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

† Ineffective or unsafe:

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

Δ Formulation failed:

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

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the

PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

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

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

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

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

* Other Reason: _____

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

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

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

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

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

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

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

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

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

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

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

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

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

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

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

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

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

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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/s/

GINA M DAVIS
10/07/2015

Wrap-up Meeting Summary
November 20, 2015

NDA 208434

Product:	**Alectinib, 150 mg capsule**
Submission Dates:	June 5, June 19 and July 6, 2015 – (Rolling Submission)
Received Date:	July 6, 2015 – clock starts
Sponsor:	Hoffmann-La Roche, Inc.
Proposed:	For the treatment of Anaplastic Lymphoma Kinase (ALK)-positive, locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC)

Agenda Items:

Primary reviewers and consultants presentations of outstanding issues

- All consults and reviews are complete except CMC. CMC is still waiting for the EIR and 483 response. The facility review will most likely be completed during the week of 12/2 – 12/6/15. CMC will provide an update on Monday November 30, 2015.

Discussion of proposed action to be taken

- The Division is still planning to take action on December 18, 2015.

Discussion of outstanding labeling issues

- The Late Cycle Meeting scheduled for today, November 20, 2015, will address any outstanding labeling issues with Hoffmann-La Roche (Roche).

Discussion Points

Status of the approval letter

- Will circulate the approval letter to the team by close of business November 20, 2015.

Status of Action Package

- The action package is up-to-date.

Postmarketing Requirements (PMRs)/Postmarketing Commitments (PMCs) – Templates

- The language for the clinical and clinical pharmacology PRMs has been reviewed and cleared by the Deputy Director for Safety. The Clinical Pharmacology template is complete and the clinical team will complete their template shortly. The CMC PMC will be discussed this afternoon at the Late Cycle Meeting with Roche.

Burst

- The will be addressed by the clinical team.

Press Release

- The substantially complete label has been sent.

The Review Team

Patricia Keegan	Division Director
Gideon Blumenthal	CDTL
Erin Larkins	Clinical
Whitney Helms	Nonclinical (TL)
Eias Zahalka	Nonclinical
Kim Ringgold	Nonclinical
Hong Zhao	Clinical Pharmacology (TL)
Stacy Shord	Clinical Pharmacology
Kun He	Biostatistics (TL)
Huanyu (Jade) Chen	Biostatistics
Olen Stephens	CMC (TL)
Charles Jewell	CMC - DS
Rajiv Agarwal	CMC - DP
Zhong Li	CMC – Facility
Zhaoyang Meng	CMC- Micro and Process
Okpo Eradiri	Biopharmaceutics (TL)
Gerlie Gieser	Biopharmaceutics
Gina Davis	RPM
Sue Kang	OSE (TL)
Latonia Ford	OSE SRPM
Suchitria Balakrishman	Maternal Health
Tamara Johnson	Maternal Health
Susan Thompson	OSI
Lauren Iacono-Connor	OSI Reviewer
Alice (Chi-Ming) Tu	DEMPA TL
Grace Jones	DMEPA Safety Evaluator
Naomi Redd	DRISK TL
Mona Patel	DRISK Reviewer
Nazia Fatima	OPDP Reviewer
Barbara Fuller	DMPP Reviewer (TL)
Nathan Caulk	DMPP Reviewer

Rosane Charlab Orbach
Yaning Wang
Jingyu (Jerry) Yu
Lynne Yao (optional)
Linda Lewis (optional)
Denise Pica-Branco (optional)
Hari Sachs
Angelica Dorantes (optional)

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/s/

GINA M DAVIS
12/10/2015

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

Memorandum

Date: December 9, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434 – Hoffmann-La Roche, – Alecensa (alectinib) – Minutes from Teleconference – Labeling Negotiations

---

Sponsor Attendees

Bogdana Ioana Balas, MD, Safety Science Leader
Llorente Bonaga, Technical Regulatory Lead
Walter Bordogna, PhD, Senior Clinical Scientist
Christiane Froehlich, Technical Development Lead
Sophie Golding, Project Lead Statistician
Samir Megateli, Lifecycle Leader
Mireille Methlin Costantzer, PharmD, Global Regulatory Leader
Peter Morcos, PharmD, Clinical Pharmacology Lead
Chez Min Murdoch, Regulatory Program Director
Josina Reddy, M.D., Ph.D., Group Medical Director
Nathan Winslow, Regulatory, Lung Franchise Head
Li Yu, PhD, DMPK Lead
Ali Zeaiter, MD, Global Development Team Leader

FDA Attendees

Patricia Keegan, M.D., Director, Division of Oncology Products 2 (DOP 2)
Gideon Blumenthal, M.D., Team Lead, DOP 2
Erin Larkins, M.D., Medical Officer
Gina Davis, M.T.
Stacy Shord
Huanyu Chen
Rowe Medina
Nazia Fatima

Background

On December 7, 2015, DOP 2 held a teleconference with Hoffmann-La Roche to discuss the Alecensa (alectinib) label and reach agreement.

Discussion

The following sections were discussed
Highlights
Indications and Usage
Adverse Reactions
Table 3
Adverse Reactions in ≥ 10% (All Grades) or ≥ 2% (Grade 3-4) of Patients in Studies 1 and 2
Table 4
Laboratory Abnormalities Occurring in >20% of Patients in Studies 1 and 2
Use in Specific Populations
Geriatric Use
Mechanism of Action
Clinical Pharmacology
Pharmacodynamics
Cardiac Electrophysiology
Clinical Studies
Table 5
Efficacy Results in Studies 1 and 2
Table 6
CNS Objective Response in Patients with Measurable CNS Lesions in Studies 1 and 2
Patient Information Sheet

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/s/

GINA M DAVIS
12/10/2015

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

Memorandum

Date: July 22, 2015

From: Patricia Keegan, M.D.,
Director, Division of Oncology Products 2

Subject: Designation of Review for Original NDA Submission

Sponsor: Hoffmann-La Roche, Inc.
Product: alectinib
Proposed indication: Alectinib is indication for the treatment of patients with anaplastic lymphoma (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

To: NDA 208434

The review status of this file submitted as a New Molecular Entity NDA is designated to be:

☐ Standard (PDUFA V - 12 Months) ☒ Priority (PDUFA V - 8 Months)

BACKGROUND

Studies NP28761 and NP28673, which were multicenter, single arm trials conducted in 87 and 138 patients with metastatic, ALK-positive NSCLC with disease progression on, or intolerance to, crizotinib demonstrated an overall response rate (ORR) of 44% (95% confidence interval [CI]: 36%, 53%) and of 38% (95% CI: 28%, 49%) with median duration of response of 7.5 months and 11.2 months as determined by an independent radiologic review committee in 87 patients (Study NP28761) and 138 patients (Study NP28673), respectively, in patients with ALK mutation-positive NSCLC that had progressed on crizotinib or who were unable to tolerate crizotinib. In the subset of 110 patients enrolled in Study NP29763 who had progressed on crizotinib and received prior platinum-based chemotherapy, ORR was 39% (95% CI: 30, 49) and the median duration of response was 10.9 months.

ASSESSMENT OF REQUEST

In evaluating the review designation for Hoffmann-La Roche's New Drug Application (NDA), I considered their rationale including the summary results of Studies NP28761 and NP28673 and the following FDA Guidance and MAPP:

- CDER MAPP 6020.3, Priority Review Policy (version 2)
- Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014)

As stated in these FDA documents (above), an application for a drug will receive priority review designation if it is for a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. In addition, specific statutory provisions

provide for priority review for various types of applications

On a case-by-case basis, FDA determines at the time of NDA, BLA, or efficacy supplement filing whether the proposed drug would be a *significant improvement* in the safety or effectiveness of the treatment, prevention, or diagnosis of a serious condition compared to available therapies.

Significant improvement may be illustrated by the following examples:

- Evidence of increased effectiveness in treatment, prevention, or diagnosis of a condition
- Elimination or substantial reduction of a treatment-limiting adverse reaction
- Documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes
- Evidence of safety and effectiveness in a new subpopulation

For purposes of determining whether a significant improvement exists over available therapy, FDA generally considers *available therapy* (and the terms *existing treatment* and *existing therapy*) as a therapy that:

- Is approved or licensed in the United States for the same indication being considered for the new drug and
- Is relevant to current U.S. standard of care (SOC) for the indication

FDA's available therapy determination generally focuses on treatment options that reflect the current SOC for the specific indication (including the disease stage) for which a product is being developed. In evaluating the current SOC, FDA considers recommendations by authoritative scientific bodies (e.g., National Comprehensive Cancer Network, American Academy of Neurology) based on clinical evidence and other reliable information that reflects current clinical practice. When a drug development program targets a subset of a broader disease population (e.g., a subset identified by a genetic mutation), the SOC for the broader population, if there is one, generally is considered available therapy for the subset, unless there is evidence that the SOC is less effective in the subset.

A drug would not be considered available therapy if the drug is granted accelerated approval based on a surrogate endpoint or an intermediate clinical endpoint and clinical benefit has not been verified by post-approval studies.

Assessment*:*
This New Drug Application (NDA) was not submitted under the statutory provisions for which priority review designation is required by statute.

Criterion 1: the drug treats a serious condition

Anaplastic lymphoma kinase (ALK) mutation-positive lung cancer accounts for approximately 5%[1] of the adenocarcinoma of the lung, which constitute approximately 85% of the 221,200 new cases of lung cancer estimated to occur in 2015 by the National Institute of Health (NIH) Surveillance, Epidemiology and End Results (SEER) Program[2], for an estimated incidence of approximately 9400 new cases of ALK mutation-positive NSCLC in the US annually. The estimated 5-year survival rate for metastatic lung cancer is less than 5% and there is no evidence

[1] *ALK*, *ROS1* and *RET* fusions in 1139 lung adenocarcinomas: A comprehensive study of common and fusion pattern-specific clinicopathologic, histologic and cytologic features. Pan Y, Zhang Y, Li Y, et also. Lung Cancer (84):121–126, 2014.
[2] http://seer.cancer.gov/statfacts/html/lungb html.

that the presence of ALK mutations confer a better prognosis.[3] [4] However, with the advance of effective therapy inhibiting kinase activation, specifically crizotinib, progression-free survival is improved as compared to first-line, platinum-based doublet chemotherapy [HR 0.45 (0.35, 0.60); median PFS 10.9 vs. 7.0 months] or second-line pemetrexed or docetaxel [HR 0.49 (0.37, 0.64); median PFS 7.7 vs. 3.0]. The median survival was 20.8 months for those receiving crizotinib as second-line therapy.[5,6]

I concur that the indicated population has a serious, life-threatening condition.

Criterion 2: the drug would be a *significant improvement* in the safety or effectiveness of the treatment, prevention, or diagnosis compared to available therapies

FDA approved therapy for the second-line treatment of NSCLC that have been evaluated in patients with ALK mutation-positive NSCLC:

- Docetaxel or pemetrexed as second-line chemotherapy following platinum-based doublet chemotherapy. In patients with ALK-mutation-positive NSCLC receiving second-line therapy in a randomized trial comparing the efficacy of platinum-based chemotherapy with crizotinib, demonstrated an ORR of 20% (14, 26) with a median duration of response of 5.6 months.

The following drugs are FDA-approved regimens for the second-line treatment of NSCLC.

- Ramucirumab with docetaxel has not been evaluated in studies of ALK mutation-positive NSCLC. In studies of patients with NSCLC receiving second-line chemotherapy, after platinum-based doublet chemotherapy, the ORR was 23% (95% CI: 20, 26) in patients randomized to ramucirumab plus docetaxel and 14% (95% CI: 11, 17) in patients receiving placebo plus docetaxel.[7]

- Nivolumab has not been evaluated in studies of ALK mutation-positive NSCLC. In studies of patients with NSCLC receiving second-line chemotherapy, after platinum-based doublet chemotherapy, the ORR was 19% (95% CI: 15, 24) in patients randomized to nivolumab and 12% (95% CI: 9, 17) in patients randomized to docetaxel.

There are no FDA-approved drugs that are specifically indicated for the treatment of patients with ALK-mutation- positive NSCLC who are no longer responding to or are intolerant of crizotinib.

- Ceritinib, which is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib, was approved under the provisions of 21 CFR 314 Subpart H; thus ceritinib is not considered to be available therapy as the clinical benefit of the durable ORR observed with ceritinib has not been verified.

NCCN Practice Guidelines: The National Comprehensive Cancer Network (NCCN) clinical practice guidelines recommend ceritinib for the treatment of patients with metastatic ALK-positive NSCLC who have progressed on crizotinib or are intolerant of crizotinib.

---

[3] *ALK*, *ROS1* and *RET* fusions in 1139 lung adenocarcinomas: A comprehensive study of common and fusion pattern-specific clinicopathologic, histologic and cytologic features. Pan Y, Zhang Y, Li Y, et also. Lung Cancer (84):121–126, 2014.

[4] Clinical characteristics associated with ALK rearrangements in never-smokers with pulmonary adenocarcinoma. Sun JM, Lira M, Pandya K, et al. Lung Cancer (83) 259–264, 2014.

5 http://www.accessdata fda.gov/drugsatfda_docs/label/2015/202570s014lbl.pdf

6 http://www.accessdata fda.gov/drugsatfda_docs/label/2015/125477s011lbl.pdf

7 http://www.accessdata fda.gov/drugsatfda_docs/label/2015/125477s011lbl.pdf

As noted in FDA's Guidance for Industry (referenced above) "Generally, if there is an available therapy (see section III.B.), sponsors should compare their investigational drug to the available therapy in clinical testing with an attempt to show superiority relating to either safety or effectiveness. Alternatively, sponsors could show the drug's ability to effectively treat patients who are unable to tolerate, or whose disease failed to respond to, available therapy or show that the drug can be used effectively with other critical agents that cannot be combined with available therapy."

Alectinib was not compared directly to FDA-approved therapy in clinical trials, however based on determination of ORR in two multicenter trials, as determined by an independent review committee, alectinib has demonstrated a numerically higher response rate (ORR) than was demonstrated in clinical trials reviewed by FDA for other drugs approved broadly for the second-line treatment of NSCLC (docetaxel alone or with ramucirumab, pemetrexed, and nivolumab). Specifically, the lower bound of the 95% confidence limit around the observed ORR for alectinib excludes the upper bound of the 95% confidence limit around the observed ORR for these second-line treatment regimens. Based on these data, I conclude that alectinib provides a significant improvement in a clinically important and durable overall response rate as compared to that demonstrated in clinical studies of nivolumab, docetaxel, docetaxel plus ramucirumab, and pemetrexed.

Recommendation: Priority Review

Based on the information described above, I have concluded that alectinib has demonstrated a significant improvement in overall response rate over available therapy for the treatment of patients with anaplastic lymphoma (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

{See appended electronic signature page}

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

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/s/

PATRICIA KEEGAN
12/10/2015

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

Memorandum

Date: December 9, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434 – Hoffmann-La Roche – Alecensa (alectinib) – FDA proposed labeling

---

Dear Ms. Murdoch:

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

We also refer to the December 8, 2015, electronic (email) communication containing your proposal to the package insert (PI) and patient package insert (PPI) for the product alectinib. We have reviewed your proposal and have provided edits.

Please review, make necessary edits, and provide a response as soon as possible. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
FDA proposed labeling

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

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/s/

GINA M DAVIS
12/09/2015

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

Memorandum

Date: December 7, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434 – Hoffmann-La Roche – Alecensa (alectinib) – FDA proposed labeling

---

Dear Ms. Murdoch:

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

We also refer to your November 25, 2015, amendment regarding the counter-proposal to the Alecensa (alectinib) package insert (PI). We have reviewed your submission and include our proposal to the PI as well as an updated patient package insert (PPI). Please review the PI and PPI for discussion at this afternoon's teleconference.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
FDA proposed labeling

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/s/

GINA M DAVIS
12/07/2015

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

Memorandum

Date: December 7, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434 – Hoffmann-La Roche – Alecensa (alectinib) – FDA proposed labeling

---

Dear Ms. Murdoch:

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

Please also refer to the December 7, 2015, teleconference with your team. Enclosed is the package insert and patient package insert discussed at this afternoon's meeting.

Please review, make necessary edits, and provide a response by noon Wednesday, December 9, 2015. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
FDA proposed labeling

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GINA M DAVIS
12/07/2015

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

Memorandum

Date: December 1, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434 Hoffmann-La Roche – Alecensa (alectinib) – FDA response to Roche's request for information regarding the proposed postmarketing commitment

---

Dear Ms. Murdoch:

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

We also refer to your November 24, 2015, amendment regarding the proposed Postmarketing Commitment (PMC) for a (b) (4) We have reviewed your submission and have the following comment.

> We agree with your proposal to retain the packaging configuration as described in NDA 208434 (b) (4) . However, if any post-marketing cases associated with prescribing errors, dispensing errors, or complaints occur; then we will request that you address these errors/complaints, (b) (4)

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
12/01/2015

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

Memorandum

Date: December 1, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434 Hoffmann-La Roche – Alecensa (alectinib) – FDA request for information – Carton and Container Labeling

---

Dear Ms. Murdoch:

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

We also refer to your November 20, 2015, amendment in response to our November 18, 2015, information request regarding the carton and container labels for your product alectinib.

> We have reviewed your submission and find your responses acceptable. Please submit final carton and container labeling for alectinib.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
12/01/2015

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

Memorandum

Date: November 20, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434 – Hoffmann-La Roche – Alecensa (alectinib) – FDA proposed labeling

---

Dear Dr. Tao:

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

Please also refer to the FDA proposal to the Alecensa (alectinib) package insert (PI) sent on November 20, 2015, via electronic (email) communication just prior to the Late Cycle Meeting. This memorandum includes that PI and serves as a formal submission. Please review the PI and provide a counter- proposal on or before Wednesday, November 25, 0215.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
FDA proposed labeling

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/s/

GINA M DAVIS
11/20/2015

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

Memorandum

Date: November 18, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434 Hoffmann-La Roche – Alecensa (alectinib) – FDA request for information

---

Dear Dr. Tao:

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

Currently your application is under review and we have the following comments and requests for information.

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".

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

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/s/

GINA M DAVIS
11/18/2015

MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 10, 2015
TIME: 12:00 PM – 1:00PM
LOCATION: CDER WO 22- Room 4266
APPLICATION: NDA 208434
DRUG NAME: Alecensa (alectinib)
TYPE OF MEETING: Late Cycle Meeting – Internal Meeting
MEETING CHAIR: Patricia Keegan, M.D.
MEETING RECORDER: Gina Davis

FDA ATTENDEES:
Patricia Keegan, Patricia, Division of Oncology Products 2
Gideon Blumenthal, Division of Oncology Products 2
Erin Larkins, Division of Oncology Products 2
Gina Davis, Division of Oncology Products 2
Leslie Doros, Division of Oncology Products 2
Whitney Helms, Division of Hematology Oncology Toxicology
Eias Zahalka, Division of Hematology Oncology Toxicology
Stacy Shord, Division of Clinical Pharmacology V
Hong Zhao, Division of Clinical Pharmacology V
Huanyu (Jade) Chen, Division of Biostatistics V
Olen Stephens, Division of New Drug Quality Assessment
Rajiv Agarwal, Division of New Drug Quality Assessment
Carolyn McCloskey, of Surveillance and Epidemiology
Grace Jones, Office of Surveillance and Epidemiology
Latonia Ford, Office of Surveillance and Epidemiology

BACKGROUND:

On July 6, 2015, Hoffmann-La Roche (Roche) submitted a New Drug Application (NDA) to the Division of Oncology Products 2 (DOP 2) for their product Alecensa (alectinib) for the treatment of ALK Positive NSCLC. This meeting was scheduled to review the agenda and Late Cycle Meeting Package that will be sent to Roche in preparation for the November 20, 2015, Late Cycle Meeting (LCM).

MEETING OBJECTIVES:

- Identify any key issues that will be discussed at the LCM.

DISCUSSION POINTS:

- No substantive review issues, no risk management actions, and no plans for an Advisory Committee meeting are associated with this application.

- In an electronic (email) communication, dated November 6, 2015, Roche requested that their counter-proposal to the Alecensa (alectinib) package insert be discussed during a teleconference prior to the November 20, 2015, face to face LCM. Those issues are listed below;

    - Indication statement: inclusion of patients who are intolerant to crizotinib
    - Section 14, Table 5: ORR and DoR by ITT
    - Section 16, storage in the original container

- [redacted] (b) (4)

DECISIONS (AGREEMENTS) REACHED:

The following topics will be discussed in detail at the LCM;

- Roche's counter-proposal to the Alecensa (alectinib) label
- [redacted] (b) (4)

ACTION ITEMS:

- DOP 2 will send the LCM Package to the Roche on or before Friday, November 13, 2015.

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/s/

GINA M DAVIS
11/13/2015

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

Memorandum

Date: November 9, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434 – Hoffmann-La Roche – Alecensa (alectinib) - Late Cycle Meeting Package

---

Dear Dr. Tao,

The Division of Oncology Products 2 has scheduled a late cycle teleconference/meeting with Hoffmann-La Roche, Inc. to discuss the status of the review.

You will receive the Late Cycle Meeting Package during the week of November 8 - 13, 2015. If you have any additional questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
11/09/2015

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

Memorandum

Date: November 5, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434 – Hoffmann-La Roche – Alecensa (alectinib) – FDA proposed labeling

---

Dear Dr. Tao:

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

> We also refer to the Alecensa (alectinib) package insert (PI) submitted with your application. Attached to this memorandum is our proposal to your PI. Please review and provide feedback. Please note, the Office of Prescription Drug Promotion and the Division of Medical Policy Programs are currently reviewing the PI and may have additional edits and comments.

Please provide a response by close of business November 12, 2015. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
FDA proposed labeling

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

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/s/

GINA M DAVIS
11/05/2015

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

Memorandum

Date: October 30, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434– Hoffmann-La Roche, Inc. – Alecensa (alectinib) –request for information

---

Dear Dr. Tao:

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

Currently your application is under review and we have the following comments and requests for information.

Please submit the efficacy analysis results as summarized in the Tables 1-2 for the as treated (AT) analysis set in both studies (NP28673 with Jan 2015 data cut-off and NP28761 with Oct 2014 data cut-off) by COB Friday.

Table 1. Efficacy Results per IRC Assessment, AT Analysis Set

	NP28673* **(N=138)**	**NP28761**** **(N=87)**
DoR (month)		
PD, n (%)		
Median (95% CI)		
Duration of Treatment, Median (95% CI)		
Duration of Follow Up, Median (95% CI)		

* NP28673 with Jan 2015 data cut-off

** NP28761 with Oct 2014 data cut-off

Table 2. Subgroup ORR Results per IRC Assessment, AT Analysis Set

	NP28673* (N=138)		**NP28761** (N=87)**	
	N	ORR (95% CI)	N	ORR (95% CI)
AGE: < 65				
>= 65				
Race: White				
Asian				
Other				
Sex: Male				
Female				
CNS ORR				
Measurable CNS ORR				
Prior Brain Radiation				

* NP28673 with Jan 2015 data cut-off
** NP28761 with Oct 2014 data cut-off

Please provide a response to the aforementioned requests by close of business Friday, October 30, 2015 but no later than noon (EST) on Monday November 2, 2015. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
10/30/2015

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

Memorandum

Date: October 29, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434– Hoffmann-La Roche, Inc. – Alecensa (alectinib) –request for information

---

Dear Dr. Tao:

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

Currently your application is under review and we have the following comments and requests for information.

Please submit the efficacy analysis results as summarized in the Tables 1-3 for the as treated (AT) analysis set in both studies (NP28673 with Jan 2015 data cut-off and NP28761 with Oct 2014 data cut-off) by COB Friday.

Table 1. Efficacy Results per IRC Assessment, AT Analysis Set

	NP28673* **(N=138)**	**NP28761**** **(N=87)**
DoR (month)		
PD, n (%)		
Median (95% CI)		
Duration of Treatment, Median (95% CI)		
Duration of Follow Up, Median (95% CI)		

* NP28673 with Jan 2015 data cut-off

** NP28761 with Oct 2014 data cut-off

Table 2. Subgroup ORR Results per IRC Assessment, AT Analysis Set

	NP28673* (N=138)		**NP28761** (N=87)**	
	N	ORR (95% CI)	N	ORR (95% CI)
AGE: < 65				
>= 65				
Race: White				
Asian				
Other				
Sex: Male				
Female				
CNS ORR				
Measurable CNS ORR				
Prior Brain Radiation				

* NP28673 with Jan 2015 data cut-off
** NP28761 with Oct 2014 data cut-off

Please provide a response to the aforementioned requests by close of business Friday, October 30, 2015. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
10/29/2015

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

Memorandum

Date: October 26, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434 Hoffmann-La Roche – alectinib(proposed proprietary name Alecensa) – FDA request for information

---

Dear Dr. Tao:

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

Currently your application is under review and we have the following comment and request for information.

> If a patient undergoes one or two dose reductions, how will a pharmacist dispense a 30 day supply (less than 240 capsules) given the requirement to store the proposed capsule in the original container? Please advise.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
10/26/2015

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

Memorandum

Date: October 23, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434– Hoffmann-La Roche, Inc. – Alecensa (alectinib) –request for information

---

Dear Dr. Tao:

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

Currently your application is under review and we have the following comment and request for information.

1. From review of the protocols for Studies NP28761 and NP28673, it appears that recommendations to avoid prolonged sun exposure and use sunscreen related to the risk of phototoxicity with alectinib were added to these protocols in Version 6.0 and Version 3.0, respectively. Please provide the following information:

   Incidence of phototoxicity in each study during the time periods before and after implementation of these protocol versions.

Please provide a response to the aforementioned request by October 28, 2015. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
10/23/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208434

MID-CYCLE COMMUNICATION

Hoffmann-La Roche Incorporated
c/o Genentech, Inc.
Attention: Chung Ying Tao, Ph.D.
Associate Program Director, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080

Dear Dr. Tao

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Alecensa (alectinib) capsule, 150 mg.

We also refer to the teleconference between representatives of your firm and the FDA on October 14, 2015. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Gina Davis, Senior Regulatory Health Project Manager at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Gideon Blumenthal, M.D.
Cross Discipline Team Lead
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Minutes from the Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: **October 14, 2015 – 2:00 PM – 3:00 PM**

Application Number: NDA 208434
Product Name: Alecensa (alectinib)
Indication: Treatment of ALK positive NSCLC
Applicant Name: Hoffmann-La Roche, Inc. (Roche)
Meeting Chair: Gideon Blumenthal, M.D.
Meeting Recorder: Gina Davis

FDA ATTENDEES

Division of Oncology Products 2 (DOP 2)
Patricia Keegan, M.D., Director, DOP 2
Gideon Blumenthal, M.D., Medical Team Lead, DOP 2
Erin Larkins, M.D., Medical Officer, DOP 2
Jennie Chang, PharmD., Clinical Analyst, OHOP/DOP 2
Gina Davis, M.T. Senior Regulatory Health Project Manager, DOP 2

Division of Hematology Oncology Toxicology (DHOT)
Whitney Helms, Ph.D., Nonclinical Supervisor, DHOT
Eias Zahalka, Ph.D., Nonclinical Reviewer, DHOT

Division of Biostatistics (DB V)
Huanyu (Jade) Chen, Ph.D., Statistical Reviewer, DB V
Kun He, Ph.D., Statistical Team Lead, DB V

Division of Clinical Pharmacology V (DCP V)
Stacy Shord, PhamD., Clinical Pharmacology Reviewer, DCP V
Hong Zhao, Ph.D., Clinical Pharmacology Team Lead, DCP V

Office of Product Quality (OPQ)
Olen Stephens, Ph.D., Branch Chief, OPQ

Office of Surveillance and Epidemiology (OSE)
Latonia Ford, BSN, MBA, Safety Regulatory Project Manager,
Office of Surveillance and Epidemiology

APPLICANT ATTENDEES

Ali Zeaiter, M.D., Global Clinical Science Lead
Walter Borgdona, Ph.D., Senior Clinical Scientist
Bogdana Balas, M.D., Safety Science Lead
Sophie Golding, Ph.D., Project Lead Statistician
Petra Buse, Ph.D., Biometrics Submission Team Lead
Peter Morcos, PharmD., Clinical Pharmacology Lead
Li Yu, Ph.D., Nonclinical DMPK Lead
Sven Kronenberg, Ph.D., Nonclinical Toxicology Lead
Christiane Froehlich, Ph.D., Technical Development Lead
Mireille Methlin Costantzer, PharmD, Global Regulatory Lead
Florence Tao, Ph.D., US Regulatory Partner
Nathan Winslow, Regulatory Franchise Director
Kin Tang, Ph.D., R.Ph., Technical Regulatory Group Director
Robin Taylor, Lung & Cancer Immunotherapy Franchise Head

SPONSOR SILENT LISTENERS

Shailise Ross, US Regulatory Intern
Negar Sadrzadeh, Ph.D., US Technical Regulatory
Sandra Nino-Siddens, US Regulatory Team Leader
Jerald Grace, US Regulatory
Nitzan Sternheim, US Regulatory
Kazuo Semitsu, US Labeling
Emily Bussiere, US Labeling
Lisa Kelsey, US Labeling
Nicole Fitzpatrick, Medical Science Director

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

Currently there are no significant issues regarding the following disciplines;

- Clinical
- Statistics
- Clinical Pharmacology
- Nonclinical
- CMC

3.0 INFORMATION REQUESTS

- Clinical/Stats IR regarding Study NP28673 and Study NP28761 sent October 7, 2015.

  Discussion during the teleconference: Roche provided an electronic (email) communication on October 14, 2015, to FDA's October 7, 2015, request for information regarding Study NP28673 and Study NP28761. The response was reviewed by the FDA and deemed acceptable. Roche will formally submit an amendment to the NDA.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

- Currently there are no plans for a REMs.

  Discussion during the teleconference: Roche acknowledged our response and no discussion occurred.

5.0 ADVISORY COMMITTEE MEETING

- Currently there are no plans to hold an Advisory Committee Meeting.

  Discussion during the teleconference: Roche acknowledged our response and no discussion occurred.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

- The proposed date for the late cycle meeting is November 20, 2015.

  Discussion during the teleconference: Roche requested a face to face meeting on November 23, 2015, but scheduling conflicts with the FDA would not allow for this change. FDA will maintain the November 20, 2015 late cycle meeting date and the meeting will be a face to face meeting. FDA intends to send the briefing package to you approximately 12 days in advance of the meeting. If these timelines change, FDA will communicate updates to Roche during the course of review.

- **PROPOSED POSTMARKETING COMMITMENTS (PMC)/POSTMARKETING REQUIREMENTS (PMR)**

Clinical - PMR

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

Final Protocol Submission
Study/Trial Completion:
Final Report Submission:

Clinical pharmacology - PMR

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

Final Protocol Submission
Study/Trial Completion:
Final Report Submission:

Please provide milestone dates for the following PMRs by October 31, 2015. Please note exact wording of the PMRs listed below are subject to change.

Discussion during the teleconference: Roche acknowledged the PMC/PMR requests and agreed to provide milestone dates on or before October 31, 2015.

ADDITIONAL COMMENTS

ACTION DATE

- Roche asked FDA if an approval date for alectinib was on the calendar.

Discussion during the teleconference: FDA stated that an approval date for alectinib is not on the calendar at this time but a response to the question could potentially be provided at the late cycle meeting. Roche acknowledged FDA's response and no further discussion occurred.

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/s/

GIDEON M BLUMENTHAL
10/21/2015

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

Memorandum

Date: October 20, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434– Hoffmann-La Roche, Inc. – Alecensa (alectinib) –request for information

---

Dear Dr. Tao:

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

Currently your application is under review and we have the following comments and requests for information.

1. Based on the Laboratory Test Results Shift Table on page 727 of the 90-Day Safety Update, 10 patients (4.6%) had Grade 3 elevations of CPK (2 of these without baseline CPK data available). Please provide the following information for each these patients:

   - Subject ID
   - List of values for CPK and creatinine throughout treatment
   - Presence or absence of musculoskeletal symptoms
   - Any dose modifications made as a result of CPK elevation

2. Please provide separate listings for numbers of patients experiencing dose reduction, dose interruption, and treatment discontinuation for each of the following:

   - Elevated AST
   - Elevated ALT
   - Elevated bilirubin
   - Elevated CPK
   - Myalgia/musculoskeletal pain

   Note: For AST, ALT, bilirubin, and CPK this should be based on number of patients with documented elevations based on shifts in laboratory test results.

   Information provided should include:

   - Subject ID
   - Grade of elevation (based on laboratory data)/event leading to dose modification
   - Length of time off therapy for dose interruptions
   - Listing of relevant laboratory results ((i.e.., listing of AST, ALT, and bilirubin for patients experiencing dose reductions for liver enzyme elevations; listing of CPK and creatinine for patients experiencing dose modifications for elevated CPK or myalgia/musculoskeletal pain) throughout course of treatment.

Please provide a response by October 26, 2015. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
10/20/2015

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

Memorandum

Date: October 20, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434 – Hoffmann-La Roche – Alecensa (alectinib) - Late Cycle Teleconference/Meeting

---

Dear Dr. Tao,

The Division of Oncology Products 2 has scheduled a late cycle teleconference/meeting with Hoffmann-La Roche, Inc. to discuss the status of the review.

Late Cycle Meeting

Friday, November 20, 2015
12:00 PM – 1:00 PM

You will receive the Late Cycle Meeting Package on or before November 8, 2015. Please also complete and send in the foreign visitor forms for those individuals that are not US citizens. If you have any additional questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Forms

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH **(MM/DD/YYYY)**	
PLACE OF BIRTH **(city and country)**	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL **(**name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

GINA M DAVIS
10/20/2015

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

Memorandum

Date: October 20, 2015

From: Gina M. Davis RPM, DOP2/OHOP/CDER/FDA

Subject: Request for Information Intended to Populate the FDA Drug Trials Snapshot Website for: NDA 208434 – Alecensa (alectinib)

We are requesting your assistance in populating the attached tables for your New Molecular Entity, Alecensa, that is currently under review in the Division, this information will be posted publically, if approved, at the FDA drug snapshot website:
http://www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm

We are asking this information to allow for greater transparency by providing information to the public about participation in clinical trials for newly-approved drugs and biologics.

The website will include information on the study design, the results of efficacy and safety studies, and whether there were any differences in efficacy and side effects among sex, race, and age subgroups. It is not intended to replace or replicate the package insert, which are intended for health care practitioners, and will contain the following:

- Information written in consumer-friendly language
- Information that focus on subgroup data and analyses
- Links to PI for the product and to the FDA reviews at Drugs@FDA
- Information will be published approximately 30 days after drug/biologic approval

Therefore, we are requesting that you provide your data and complete the attached tables as well as provide descriptions of the analyses used to generate the data and any programs used to generate or analyze the data, if these are not already in the NDA submission.

We are requesting you submit this information on or before December 15, 2015.

Thank you in advance for your cooperation.

Please let me know if you have any questions.

Regards,

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager

ENCLOSURE: DTS Shelltables

PROPOSED SHELL TABLES

Table 1. Listing of Clinical Trials for the Efficacy Analysis

Study ID	No. of patients enrolled in the Drug X Arm	No. of patients enrolled in the Comparator Arm

Table 2.1 Baseline Demographics, Single or Pooled Pivotal Efficacy Trials

Demographic Parameters	**Comparator/ Control** (n=) n (%)	**Treatment Group(s)** (n=)		**Total** (n=) n (%)
		Treatment arm #1 (n=) n (%)	**Treatment arm #2** (n=) n (%)	
Sex				
Male				
Female				
Age				
Mean years (SD)				
Median (years)				
Min, max (years)				
Age Group				
<17 years				
≥17 - <65 years				
≥65 years				
≥75 years				
Race				
White				
Black or African American				
Asian				
American Indian or Alaska Native				
Native Hawaiian or Other Pacific Islander				
Other				
Ethnicity				
Hispanic or Latino				
Not Hispanic or Latino				
Region				
United States				
Rest of the World				
Canada				
South America				
Europe				
Asia				
Africa				

Source: list datasets or other sources of information

Table 2.2 Baseline Demographics, Multiple Pivotal Efficacy Trials

Demographic Parameters	Trial #1 (N=)		Trial #2 (N=)		Total (n=) n (%)
	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	
Sex					
Male					
Female					
Age					
Mean years (SD)					
Median (years)					
Min, max (years)					
Age Group					
<17 years					
≥17 - <65 years					
≥65 years					
≥75 years					
Race					
White					
Black or African American					
Asian					
American Indian or Alaska Native					
Native Hawaiian or Other Pacific Islander					
Other					
Ethnicity					
Hispanic or Latino					
Not Hispanic or Latino					
Region					
United States					
Rest of the World					
Canada					
South America					
Europe					
Asia					
Africa					

Source: list datasets or other sources of information

Table 3 Subgroup Analysis of Primary Endpoint, Pivotal Efficacy Trials

Demographic Subgroup	Trial #1 (N=)			Trial #2 (N=)		
	Comparator/control (n=) n (%)	**Treatment arm** (n=) n (%)	Difference (95% CI)	**Comparator/control** (n=) n (%)	**Treatment arm** (n=) n (%)	Difference (95% CI)
Overall Response/All patients						
Sex						
Male						
Female						
Age Group						
<17 years						
≥17 - <65 years						
≥65 years						
≥75 years						
Race						
White						
Black or African American						
Asian						
American Indian or Alaska Native						
Native Hawaiian or Other Pacific Islander						
Other						
Ethnicity						
Hispanic or Latino						
Not Hispanic or Latino						
Region						
United States						
Rest of the World						
Canada						
South America						
Europe						
Asia						
Africa						

Source: list datasets or other sources of information

Table 4 Safety Population, Size and Denominators

Safety Database for the Study Drug[1] Individuals exposed to the study drug in this development program for the indication under review N= (N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	New Drug (n=)	Active Control (n=)	Placebo (n=)
Normal Volunteers			
Controlled trials conducted for this indication[2]			
All other than controlled trials conducted for this indication[3]			
Controlled trials conducted for other indications[4]			

[1] *study drug* means the drug being considered for approval; do not include comparator arm drugs, placebo, or vehicle control in this table

[2] to be used in product's labeling

[3] if placebo arm patients switch to study drug in open label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug arm

[4] include n in this column only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review. Consider n=0 in this column if no patients treated for other indication(s) were included in this safety database.

Table 5.1 Baseline Demographics, Safety Population, Single or Pooled Trials
(If efficacy population = safety population, refer to Table 2.1 or 2.2)

Demographic Parameters	**Comparator/ Control** (n=) n (%)	**Treatment Group(s)** (n=)		**Total** (n=) n (%)
		Treatment arm #1 (n=) n (%)	**Treatment arm #2** (n=) n (%)	
Sex				
Male				
Female				
Age				
Mean years (SD)				
Median (years)				
Min, max (years)				
Age Group				
<17 years				
≥17 - <65 years				
≥65 years				
≥75 years				
Race				
White				
Black or African American				
Asian				
American Indian or Alaska Native				
Native Hawaiian or Other Pacific Islander				
Other				
Ethnicity				
Hispanic or Latino				
Not Hispanic or Latino				
Region				
United States				
Rest of the World				
Canada				
South America				
Europe				
Asia				
Africa				

Source: list datasets or other sources of information

Table 5.2 Baseline Demographics, Safety Population, Multiple Trials

Demographic Parameters	Trial #1 (N=)		Trial #2 (N=)		Total (n=) n (%)
	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	
Sex					
Male					
Female					
Age					
Mean years (SD)					
Median (years)					
Min, max (years)					
Age Group					
<17 years					
≥17 - <65 years					
≥65 years					
≥75 years					
Race					
White					
Black or African American					
Asian					
American Indian or Alaska Native					
Native Hawaiian or Other Pacific Islander					
Other					
Ethnicity					
Hispanic or Latino					
Not Hispanic or Latino					
Region					
United States					
Rest of the World					
Canada					
South America					
Europe					
Asia					
Africa					

Source: list datasets or other sources of information

Table 6.1 Subgroup Analysis of TEAEs, Safety Population

Demographic Subgroup	Comparator/Control		Treatment		Relative Risk	95% CI	
	n (%)	Total, N	n (%)	Total, N		LL	UL
Any TEAEs							
Sex							
Male							
Female							
Age Group							
<17 years							
≥17 - <65 years							
≥65 years							
≥75 years							
Race							
White							
Black or African American							
Asian							
American Indian or Alaska Native							
Native Hawaiian or Other Pacific Islander							
Other							
Ethnicity							
Hispanic or Latino							
Not Hispanic or Latino							
Region							
United States							
Rest of the World							
Canada							
South America							
Europe							
Asia							
Africa							

Source: list datasets or other sources of information

Table 6.2 Subgroup Analysis by Sex of Common AEs, Safety Population (Events ≥ 2% of drug-treated subjects and more frequent than placebo)[1]

	Male (N=)		**Female** (N=)	
MedDRA System Organ Class Preferred Term	**Comparator/Control** (n=) n (%)	**Total Drug X** (n=) n (%)	**Comparator/Control** (n=) n (%)	**Total Drug X** (n=) n (%)
Gastrointestinal disorders				
Nausea				
Vomiting				
Diarrhea				
Abdominal pain				
General disorders/administration site conditions				
Fatigue				
Edema peripheral				
Infections and Infestations				
Influenza				
Urinary tract infection				
Injury, poisoning and procedural complications				
Fall				
Contusion				
Investigations				
Weight increased				
Blood CPK increased				
Musculoskeletal & connective tissue disorders				
Arthralgia				
Nervous system disorders				
Dizziness				
Headache				
Psychiatric disorders				
Depression				
Insomnia				
Respiratory, thoracic & mediastinal disorders				
Cough				
Skin & subcutaneous tissue disorders				
Rash				
Pruritus				

Source: list datasets or other sources of information

Example of an application-specific adverse event

Table 6.3 Subgroup Analysis by Age of Dizziness/Gait Disturbance Adverse Events, Safety Population*

	Age ≥17-<65 years (N=)		**Age ≥65 years** (N=)	
MedDRA Preferred Term	**Comparator/Control** (n=) n (%)	**Total Drug X** (n=) n (%)	**Comparator/Control** (n=) n (%)	**Total Drug X** (n=) n (%)
Dizziness				
Ataxia				
Vertigo				
Balance disorder				
Gait disturbance				
Coordination abnormal				
Cerebellar syndrome				
Cerebellar ataxia				
Vestibular ataxia				
Vestibular disorder				
Total				

*Pediatric subjects were not included in the safety population
Source: list datasets or other sources of information

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/s/

GINA M DAVIS
10/20/2015

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

Memorandum

Date: October 16, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434– Hoffmann-La Roche, Inc. – Alecensa (alectinib) –request for information

---

Dear Dr. Tao:

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

Currently your application is under review and we have the following comments and requests for information.

1. Narratives have been provided for patients who experienced Grade ≥3 elevations of AST, ALT or bilirubin reported as adverse events (n=9) in the list of narratives for patients experiencing Grade ≥3 hepatobiliary events (Section 1.6 in 90-Day Safety Update).

   Provide narratives for all patients experiencing Grade ≥3 elevations of AST, ALT or bilirubin per laboratory test results. For cases where narratives are not available, provide the CRFs for these patients. Per the Laboratory Test Results Shift Tables included in the 90-Day Safety Update this group includes 9 patients with Grade ≥3 elevations of AST (page 725), 12 for ALT (page 725), and 7 for bilirubin (page 734) (with likelihood that some patients belong to more than one group).

2. For patients in Study AF-001JP experiencing AEs classified as "rhabdomyolysis/myopathy" (SMQ) (n=35, page 191 of the CSR for Study AF-001JP), please provide the following information:

   Number of patients in this group with both elevated creatinine phosphokinase and elevated creatinine, along with narratives for these patients if available.

3. Provide any available narratives for the following subjects (all had CPK >5x ULN): Study - Center- Subject ID

   NP28673 – 91366-258185203
   NP28673 – 91998-258294201
   NP28761 – 13930-20503
   NP28761 – 12799-20302

Please provide a response by Wednesday, October 21, 2015. If you have any questions or

concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
10/16/2015

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

Memorandum

Date: October 8, 2015

From: Gina Davis, Senior Regulatory Health Project Manager, CDER/OHOP/DOP2

Subject: Agenda for Midcycle Communication - Alecensa (alectinib)

Meeting Date/Time: Wednesday, October 14, 2015 from 2:00 PM – 3:00 PM

Application Number: NDA 208434
Product Name: Alecensa (alectinib)
Indication: Treatment of ALK-Positive NSCLC
Applicant Name: Hoffmann-La Roche, Inc.
Meeting Chair: Gideon Blumenthal, M.D.
Meeting Recorder: Gina Davis

FDA TENTATIVE ATTENDEES
Gideon Blumenthal, M.D., Medical Team Lead, OHOP/DOP 2
Erin Larkins, M.D., Medical Officer, OHOP/DOP 2
Gina Davis, M.T. Senior Regulatory Health Project Manager, OHOP/DOP 2
Whitney Helms, Ph.D., Nonclinical Supervisor, OHOP/DHOT
Eias Zahalka, Ph.D., Nonclinical Reviewer, OHOP/DHOT
Kimberly Ringgold, Ph.D., Nonclinical Reviewer, OHOP/DHOT
Huanyu (Jade) Chen, Ph.D., Statistical Reviewer, OB/DB V
Kun He, Ph.D., Statistical Team Lead, OB/DB V
Stacy Shord, PhamD., Clinical Pharmacology Reviewer, OCP/DCP V
Hong Zhao, Ph.D., Clinical Pharmacology Team Lead, OCP/DCP V
Olen Stephens, Ph.D., Branch Chief, OPQ/ONDP
Charles Jewell, Ph.D., Product Quality Reviewer, OPQ/ONDP
Rajiv Agarwal, Ph.D., Product Quality Reviewer, OPQ/ONDP

SPONSOR ATTENDEES
TBA

Introductions

FDA and Hoffmann-La Roche, Inc.

Introductory Comments

Gideon Blumenthal, Cross-Discipline Team Leader

Significant Review Issues

Currently there are no significant issues regarding the following disciplines;

- Clinical
- Statistics
- Clinical Pharmacology
- Nonclinical
- CMC

Information Requests (IR)

- Clinical IR regarding Study NP28673 and Study NP28761 sent October 7, 2015.

Risk Management Update

- Currently there are no plans for a REMs

Advisory Committee Meeting Plans

- Currently there are no plans to hold an Advisory Committee Meeting.

Proposed Date for Late-Cycle Meeting

- The proposed date for the late cycle meeting is November 20, 2015.

Proposed Postmarketing Commitments (PMCs)/Postmarketing Requirements (PMRs)

- Please provide milestone dates for the following PMRs by October 31, 2015. Please note exact wording of the PMRs listed below are subject to change.

  Clinical PMR

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

  Final Protocol Submission
  Study/Trial Completion:
  Final Report Submission:

Clinical pharmacology PMR

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

  Final Protocol Submission
  Study/Trial Completion:
  Final Report Submission:

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/s/

GINA M DAVIS
10/08/2015

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

Memorandum

Date: October 7, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434– Hoffmann-La Roche, Inc. – Alecensa (alectinib) –request for information

---

Dear Dr. Tao:

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

1. A small number of patients on each study (NP28673 and NP28761) stopped their prior treatment with crizotinib for reasons other than progressive disease. Please provide response data and adverse event listings for each of these patients.

2. Please submit all CRFs for the following subjects (all had CPK >5x ULN):

   Study - Center- Subject ID
   NP28673 – 91366-258185203
   NP28673 – 91998-258294201
   NP28761 – 13930-20503
   NP28761 – 12799-20302

   If available, please also submit CRFs for the following patients from Study AF-001JP:
   Patient No.
   10101
   10203
   20203
   20702
   30401

3. Please submit the CRFs for the following subjects who experienced respiratory AEs:

Preferred Term	Study - Center - Subject ID
Pneumonia	NP28673-106909-258292201
Pneumonia	NP28673-34591-260534206
Pneumonia	NP28673-48613-258345202
Pneumonia	NP28673-91998-258294202
Pneumonia	NP28761-12799-10304
Pneumonia	NP28761-13930-20505
Pneumonia	NP28761-25142-21505
Pneumonia	NP28761-29121-20403
Pneumonia	NP28761-73182-23501
Pneumonia	NP28761-95456-10611
Pneumonia	NP28761-99462-21601
Pneumonia bacterial	NP28761-95456-10613
Lung infection	NP28673-106428-258474209
Lung infection	NP28761-12799-20301
Lung infection	NP28761-64122-21201
Lower respiratory tract infection bacterial	NP28761-27355-20707
Respiratory tract infection	NP28673-63693-258490202
Respiratory tract infection	NP28673-91366-258185202
Respiratory tract infection	NP28673-91658-258083205
Respiratory tract infection	NP28761-74062-21407

Please provide a response by Wednesday, October 14, 2015. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
10/07/2015

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

Memorandum

Date: October 5, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434– Hoffmann-La Roche, Inc. – Alecensa (alectinib) –request for information

---

Dear Dr. Tao:

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

The Division of Oncology Products 2 (DOP 2) respectfully requests a teleconference with Hoffmann-La Roche to discuss the highlights of the September 25, 2015, mid-cycle meeting. The teleconference has been scheduled for October 14, 2015 from 2:00 PM – 3:00 PM.

The following information will be discussed with you and your team.

- Any significant issues identified by the review team to date
- Any new information requests
- Information regarding major safety concerns
- Preliminary review team thinking regarding risk management
- Proposed date(s) for the late-cycle meeting
- Updates regarding plans for the AC meeting (if an AC meeting is anticipated)
- Other projected milestones dates for the remainder of the review cycle

Please provide call-in information regarding this teleconference by October 7, 2015. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
10/05/2015

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

Memorandum

Date: September 25, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434 – Hoffmann-La Roche – Alecensa (alectinib) – Mid-Cycle Meeting

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DISCUSSION

On September 25, 2015, team members assigned to the new drug application (NDA) submitted by Hoffmann-La Roche for the product Alecensa (alectinib) discussed the current findings of the application to Dr. Richard Pazdur, Head of the Office of Hematology and Oncology Products and to Dr. Patricia Keegan, Head, Division of Oncology Products 2.

Clinical

1. Is the CNS efficacy data appropriate for inclusion in the label?

   Response: Yes and No.

   Yes – The CNS efficacy data is appropriate for inclusion in the label for CORR & CDoR regarding measurable CNS disease at baseline added as secondary endpoints in later protocol versions but discussed with FDA.

   No – The CNS efficacy data is not appropriate for inclusion in the label because CR for M + NM – CORR for M+NM is an exploratory endpoint, added to one study after database lock.

2. Is prior brain radiotherapy associated with higher CNS ORR or longer CNS DoR?

   Response: No.

Clinical Pharmacology

3. Does the E-R relationships for efficacy and safety support a dosing regimen of 600 mg BID?

   Response: Yes, no E-R relationships were identified for activity endpoints or multiple safety endpoints.

4. What are the dose recommendations for patients taking strong CYP3A modulators?

Response: There are no dose modifications for patients taking strong CYP3A modulators.

Postmarketing Study

Clinical Pharmacology is proposing a postmarketing requirement to complete a pharmacokinetic trail to determine an appropriate dose of alectinib in patients with moderate and severe hepatic impairment.

Nonclinical

5. Have Pharmacology studies been submitted to support the proposed mechanism of action?

Response: Yes.

- Alectinib showed selective inhibition against ALK, ALK point mutations, RET, and RET mutants.
- CH5468924 (M4), a major metabolite, showed comparable inhibition activity on ALK, ALK mutants, RET and RET mutants to that of the parent (Point mutations inhibited were associated crizotinib resistance).
- Alectinib interacts at the ATP binding site of the ALK enzyme
- Alectinib showed inhibitory activity on human NSCLC and neuroblastoma cell lines with gene alterations of ALK.

6. Were the clinical findings predicted from the nonclinical studies?

Response: Yes, similar target organs were noted. Nonclinical findings included:

- Hematological – abnormal erythrocyte morphology (poikilocytosis), mild anemia, increased platelets; prolonged clotting time
- Gastrointestinal system: degeneration of glandular stomach epithelium and extension of proliferative zone in GI mucosa; dilation of large intestine, ileal hemorrhage
- Liver: ↑liver weight, degeneration of bile duct epithelium and hepatocytes, ↑ALP, ↑ALT, ↑AST, ↑bilirubin
- Respiratory system: alveoli hemorrhage and hemosiderin in alveolar macrophages, inflammatory cell/macrophage infiltration in alveoli and tracheal mucosa
- Phototoxic response: yes

7. Were there any nonclinical findings not evident in clinical studies?

Response:

- Adrenal gland - cortical hypertrophy; lipid droplet decrease.

- Reproductive system -
  Male: ↑testes weights, prostate and seminal vesicle glandular atrophy
  Female: ↓ovary weights, mammary gland atrophy

8. What pregnancy labeling is recommended?

Response: Pharm/Tox recommends a pregnancy warning:

- In rat and rabbit preliminary embryo-fetal studies, alectinib produced embryotoxicity at maternally toxic doses. Alectinib caused abortion, embryofetal lethality and malformations at exposures ≥3-fold the human AUC at the MRHD.

- Malformations included cardiovascular effects, dilated ureter, thymic cord, decreased fetal weights and minor skeletal anomalies.

7. Have Impurity Issues been identified?

Response: No impurities have been identified above the ICH qualification thresholds.

8. Excipient sodium lauryl sulfate (SLS)

Response: The clinical formulation containing (b) (4)% SLS showed a comparable toxicity profile to the nonclinical formulation containing no SLS in rats (i.e. no increase in GI toxicity). (b) (4)

Chemistry, Manufacturing and Controls

9. Is the proposed dissolution method is acceptable? Assessment of acceptance criteria is still pending.

Response: The proposed dissolution method is acceptable.

10. Have all the pivotal clinical lots, produced by the proposed commercial manufacturer ((b) (4)), passed dissolution testing at batch release?

Response: All the pivotal clinical lots that were produced by the proposed commercial manufacturer ((b) (4)) passed dissolution testing at batch release and under 12 months of long-term storage at 30ºC/75%RH.

ADDITIONAL COMMENTS

11. Microbiological quality was maintained throughout the study under long-term conditions (25°C/60% RH for 24 months and 30°C/75% RH for 12 months) and accelerated (40°C/75% RH for 6 months) conditions**.**

12. The microbiology section is satisfactory.

13. An Overall Manufacturing Inspection Recommendation is pending on the District Office Recommendation for the following DS/DP registration stability testing facilities:

    - Chugai Pharmaceutical Co., Ltd. (pending PAI, target for early November)

    - Chugai Pharma Manufacturing Co., Ltd. (pending PAI, target for early November)

    Based on the review of the inspectional history and district file review, all other facilities (other than the above 2 facilities) are found to be acceptable.

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GINA M DAVIS
10/05/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208434

INFORMATION REQUEST

Hoffmann-La Roche Inc.
Attention: Florence Tao, Associate Program Director, Regulatory Affairs
Genentech, a Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Tao,

Please refer to your original New Drug Application received July 16, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (Alectinib) capsule, 150 mg strength.

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

1. **Regarding the dissolution method, clarify whether the use of sinkers is being proposed. If applicable, submit a revised summary table of the dissolution method parameters and reflect the use of sinkers in the specifications table.**

2. **Regarding the dissolution acceptance criteria, FDA recommends the following:**

   Q = (b)(4)% in 30 min
   Q = % in 75 min

Submit the revised drug product specifications table reflecting the changes above changes and submit your overall response to the Information Request as an amendment to the NDA no later than COB Friday, October 9, 2015.

If you have any questions, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

Olen Stephens -S

Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Olen Stephens -S, 0.9.2342.19200300.100.1.1=2000558826
Date: 2015.09.30 10:44:57 -04'00'

Olen Stephens, Ph.D.
Branch Chief, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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

Memorandum

Date: September 29, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434 Hoffmann-La Roche – alectinib(proposed proprietary name Alecensa) – FDA request for information - CMC

Dear Dr. Tao:

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

Currently your application is under review and we have the following comment and request for information.

> Please provide a sample of the bottle, cap and desiccant for the product Alecensa. Please mail the bottle, cap and desiccant to the address listed below;
>
> Gina M. Davis, M.T.
> Food and Drug Administration
> Center for Drug Evaluation and Research
> White Oak Building 22, Room: 2306
> 10903 New Hampshire Avenue
> Silver Spring, Maryland
> Use zip code 20903 if shipping via United States Postal Service (USPS).
> Use zip code 20993 if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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GINA M DAVIS
09/29/2015

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

Memorandum

Date: September 28, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434– Hoffmann-La Roche, Inc. – Alecensa (alectinib) –request for information

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Dear Dr. Tao:

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

Currently your application is under review and we have the following comment and request for information.

> In the population PK and PK/PD Report titled "Population Pharmacokinetic Analysis and Exposure-Efficacy and -Safety Analyses of Alectinib and M4 of Phase I/II Studies NP28673 and NP28761 in Patients with ALK-Positive Non-Small Cell Lung Cancer Previously Treated with Crizotinib", the following safety parameters were selected for analyses: liver laboratory elevations: alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin; abnormal kidney function; gastrointestinal (GI) disorder; and muscular AE and creatine phosphokinase (CPK) elevation. Table 4 indicates that the efficacy and safety dataset included GIAE, MCAE, KIDAE, ASTAE, ALTAE, and TBLAE variables with each variable graded on a scale of 0 to 4.
>
> For each safety parameter, FDA has the following information request:
>
> - Identify the laboratory parameter or adverse event used to define the parameter (e.g., creatinine clearance or serum creatinine for abnormal renal function).
> - Provide the definition for each grade and indicate how each parameter was dichotomized for the analyses (i.e., normal vs. above the upper limit of normal).

Please provide a response to the aforementioned request by close of business September 30, 2015 or sooner. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
09/28/2015

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

Memorandum

Date: September 28, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434– Hoffmann-La Roche, Inc. – Alecensa (alectinib) –request for information

---

Dear Dr. Tao:

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

Please also refer to our September 16, 2015, electronic (email) communication requesting additional information and to your September 20, 2015, email requesting clarification of our information request. Lastly, please refer to the teleconference between Dr. Erin Larkins and Dr. Chung-ying Tao on September 25, 2015 requesting you formally submit the SAS programs and program documents for the cut-off as outlined below.

> Please submit the IRC efficacy analyses for the intent-to-treat (ITT) population in both studies (NP28673 with Jan 2015 data cut-off and NP28761 with Oct 2014 data cut-off). Along with the results of these analyses, please submit SAS program(s) and program document(s) for these analyses.

Please provide a response to the aforementioned request as soon as possible. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
09/28/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208434 **INFORMATION REQUEST**

Hoffmann-La Roche Inc.
Attention: Florence Tao, Associate Program Director, Regulatory Affairs
Genentech, a Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Tao,

Please refer to your original New Drug Application received July 16, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (Alectinib) capsule, 150 mg strength.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response prior to COB Wednesday, October 7, 2015.

Since the finished drug product's Assay/Content limit of Alectinib HCl for release is (b) (4)% of label claim, please tighten the current Content limit of Alectinib HCl by HPLC (b) (4)%, Table 4, Response to FDA request for information (9/17/2015)) for the final (b) (4) to be consistent with the finished drug product Assay specification.

If you have any questions, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

Olen Stephens -S

Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Olen Stephens -S, 0.9.2342.19200300.100.1.1=2000558826
Date: 2015.09.22 13:40:37 -04'00'

Olen Stephens, Ph.D.
Branch Chief, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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

Memorandum

Date: September 16, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434– Hoffmann-La Roche, Inc. – Alecensa (alectinib) –request for information

---

Dear Dr. Tao:

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

Currently your application is under review and we have the following comments and requests for information.

1. Please provide the following information:

    a. SAS program(s), program document(s) and updated analysis results (CSR Tables 3-19 and Tables 20-23) based on a 08 January 2015 data cutoff for Study NP28673 on the safety population (N=138).

    b. SAS program(s), program document(s), and analysis results (CSR Tables 6-28 and Tables 30-33) for Study NP28761 on the safety population (N=87).

2. Please also refer to Study NP28673. Please provide information on reasons for stopping crizotinib prior to trial enrollment (i.e., number of patients who stopped due to progressive disease vs intolerance).

Please provide a response to the aforementioned requests as soon as possible. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
09/16/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208434

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Hoffmann-La Roche Inc.
c/o Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

ATTENTION: Chung Ying (Florence) Tao, PhD
Associate Program Director, Regulatory Affairs

Dear Dr. Tao:

Please refer to your New Drug Application (NDA) dated and received July 6, 2015, submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Alectinib Capsules, 150mg.

We also refer to your correspondence, dated and received July 9, 2015, requesting review of your proposed proprietary name, Alecensa.

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

If any of the proposed product characteristics as stated in your July 9, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Latonia Ford, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4901. For any other information regarding this application, contact Gina Davis, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

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

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/s/

TODD D BRIDGES
09/10/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208434 **INFORMATION REQUEST**

Hoffmann-La Roche Inc.
Attention: Florence Tao, Associate Program Director, Regulatory Affairs
Genentech, a Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Tao,

Please refer to your original New Drug Application received July 16, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (Alectinib) capsule, 150 mg strength.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response prior to COB Wednesday, October 7, 2015.

Since the finished drug product's Assay/Content limit of Alectinib HCl for release is (b) (4)% of label claim, please tighten the current Content limit of Alectinib HCl by HPLC (b) (4)%, Table 4, Response to FDA request for information (9/17/2015)) for the final (b) (4) to be consistent with the finished drug product Assay specification.

If you have any questions, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

Olen Stephens -S

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Olen Stephens, Ph.D.
Branch Chief, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208434 **INFORMATION REQUEST**

Hoffmann-La Roche Inc.
Attention: Florence Tao, Associate Program Director, Regulatory Affairs
Genentech, a Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Tao,

Please refer to your original New Drug Application received July 16, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alectinib capsule, 150 mg strength.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response prior to COB Tuesday, September 29, 2015.

1. **All batches originating from the E11 campaign were manufactured using the new time-based endpoint control strategy (b) (4) Please clarify the scale of these batches. Additionally, please provide a tabular summary of the CQAs achieved for each batch.**

2. **Please specify the holding time for the final (b) (4) before the (b) (4) step as well as capsules stored in the bulk package and submit supporting data, as appropriate, to justify these proposed hold times.**

If you have any questions, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

Olen Stephens -S

Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Olen Stephens -S, 0.9.2342.19200300.100.1.1=2000558826
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Olen Stephens, Ph.D.
Branch Chief, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208434

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Hoffmann-La Roche Incorporated
c/o Genentech, Inc.
Attention: Chung Ying Tao, Ph.D.
Associate Program Director, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080

Dear Dr. Tao:

Please refer to your New Drug Application (NDA) dated July 6, 2015, received July 6, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for alectinib (proposed proprietary name Alecensa), capsule, 150 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR NDA 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is March 4, 2016. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

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

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 6, 2015. This date conforms to the 21st Century Review timeline for your application. If our review continues on an expedited timeline, we may communicate revised dates for labeling and postmarketing requirement/commitment requests.

In addition, the planned date for our internal mid-cycle review meeting is September 25, 2015. We are not currently planning to hold an advisory committee meeting to discuss this application.

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

PRESCRIBING INFORMATION

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified labeling issues, which are identified as labeling comments and/or questions in the enclosed label.

We request that you resubmit labeling (in both clean and redlined (track changes shown) Microsoft Word format) that addresses these issues by September 17, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

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

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

PROMOTIONAL MATERIAL

We will review this application under the provisions of 21 CFR 314 Subpart H – *Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses*. Unless we otherwise inform you, as required by 21 CFR 314.550, you must submit during the preapproval review period

copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). During the preapproval review period, please submit, in triplicate, a detailed cover letter (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

Because none of these criteria apply to your application, you are exempt from this requirement. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

If you have any questions, call Gina. Davis, Senior Regulatory Health Project Manager, at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Aelctinib 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/

PATRICIA KEEGAN
09/04/2015

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

Memorandum

Date: September 1, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434– Hoffmann-La Roche, Inc. – alectinib (proposed proprietary name Alecensa) –- Nonclinical – Exposure Margins

---

Dear Dr. Tao:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for "alectinib (proposed proprietary name Alecensa)."

Currently your application is under review and we have the following comment and request for information.

> Provide detailed calculations used to generate the safety margins listed in your proposed label under sections 5.5, 8.1, 13.1 and 13.2, and location of datasets used to derive values.

Please provide a response by close of business September 9, 2015. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
09/01/2015

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

Memorandum

Date: August 31, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434– Hoffmann-La Roche, Inc. – alectinib (proposed proprietary name Alecensa) – Request for information - Clinical Pharmacology

---

Dear Dr. Tao:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for "alectinib (proposed proprietary name Alecensa)."

Please also refer to the report entitled "Population PK and PK-PD Analyses Report 1064536 (alectinib)" (NDA 208434). Conduct the following analysis and submit a report with datasets and analysis code in 10 business days.

1. Multivariate logistic regression analysis to evaluate the exposure-response (E-R) relationship for efficacy endpoints (i.e., ORR, CNS ORR) to adjust for prognostic factors.

2. For Figure 32 and Figure 33, explore E-R relationship for SAEs and AEs that are not GI disorders.

3. For Figure 40, explore E-R relationship for each specific GI disorder, including constipation, diarrhea, nausea and vomiting.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
08/31/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208434 **INFORMATION REQUEST**

Hoffmann-La Roche Inc.
Attention: Chez Min Murdoch, Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Mr Murdoch,

Please refer to your original New Drug Application received 208434 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alectinib capsule 150 mg strength.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response prior to COB Tuesday, September 08, 2015.

During a recent FDA inspection of (b) (4) drug substance manufacturing facility in (b) (4) for this NDA, our field investigator found that the Alectinib drug substance stability data submitted in the NDA filing was not generated by (b) (4) (b) (4). Provide the information about the facility(ies) for the registration stability testing of both Alectinib drug substance and drug product. Update the 356h form, and Sections 3.2.S.2.1 and 3.2.P.3.1 accordingly.

If you have any questions, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

Olen Stephens -S

Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Olen Stephens -S, 0.9.2342.19200300.100.1.1=2000558826
Date: 2015.08.19 10:13:59 -04'00'

Olen Stephens, Ph.D.
Branch Chief, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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

Memorandum

Date: August 11, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434– Hoffmann-La Roche, Inc. – alectinib (proposed proprietary name Alecensa) – Stats request for information

---

Dear Ms. Murdoch:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for "alectinib (proposed proprietary name Alecensa)."

Currently your application is under review and we have the following comment and request for information.

Please provide the following information:

- Executable SAS program(s) with adequate document(s) to duplicate the analysis datasets derivation from raw datasets.

- SAS programs as well as format library files used for efficacy and safety data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs.

- SAS programs with adequate document(s) for the derived datasets and the analyses associated with the results presented in the proposed package insert.

Please provide a response as soon as possible. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
08/11/2015

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

Memorandum

Date: August 11, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434– Hoffmann-La Roche, Inc. – alectinib (proposed proprietary name Alecensa) – Request for information - Clinical Pharmacology

---

Dear Ms. Murdoch:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for "alectinib (proposed proprietary name Alecensa)."

Currently your application is under review and we have the following comments and requests for information.

1. Resubmit all files submitted along with the population pharmacokinetic and exposure-response study report with a ".txt" extension, as the files with this extension appear damaged and not readable.

2. Repeat alectinib-repaglinide drug-drug interaction (DDI) physiological-based pharmacokinetic (PBPK) simulations using final integrated alectinib-M4 model. Presentation of the final integrated model can be organized in a step-wise manner.

    A. Model development in healthy subjects

        i. Develop alectinib and M4 models using in vitro metabolism data, in-silico data (e.g., Kp from Gastroplus modeling), and results from human mass-balance study (including oral and intravenous data). Assumptions on fm,CYP3A for alectinib can be based on hepatocyte data, mass balance data, and differential absolute bioavailability data (capsule vs suspension). Clarify if assumptions on fm,CYP3A for M4 can be made based on in vitro data.

        ii. Conduct multiple dose simulations in patients using the NSCLC populations to justify the need to (1) adjust intrinsic clearance values in patients (or: Can pharmacokinetic (PK) differences be represented by simulations using the same drug model in healthy subjects and NSCLC patients?) and (2) consider time-dependent inhibition (TDI) and/or induction of CYP3A in the integrated model. At this stage, a model with no CYP3A interaction mechanisms by alectinib and M4 and a model with concurring TDI and induction potential are expected to predict similar PK profiles of alectinib and M4.

B. Verify and confirm the model regarding assumptions on fm,CYP3A of alectinib, fm,CYP3A of M4 and autoinhibition and/or induction of CYP3A.

i. Prospectively simulate the effects of posaconazole and rifampin. Modify rifampin model using the strategy for posaconazole model and refer to Xu et al (Drug Metabo Dispo, 39:1139-48; 2011).

ii. Prospectively simulate the effect of alectinib/M4 on midazolam in NSCLC patients.

Submit model files and excel output files being used to generate final results of above simulations. Software specific files (.cmp, .lbr, and .wks) should be executable by FDA reviewer using SimCYP software (version 13, release 2).

3. Provide an assessment of adverse event rates and dose modification frequencies for patients with moderate renal impairment and patients with mild renal impairment compared to patients with normal renal function. Propose corresponding labeling statements based on this assessment.

Please provide a response by close of business August 21, 2015. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
08/11/2015

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

Memorandum

Date: August 11, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434– Hoffmann-La Roche, Inc. – alectinib (proposed proprietary name Alecensa) – Request for information - Clinical Pharmacology

---

Dear Ms. Murdoch:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for "alectinib (proposed proprietary name Alecensa)."

Currently your application is under review and we have the following comment and request for information regarding your August 9, 2015 electronic (email) communication.

> The ECG waveform files in the ECG warehouse are linked to those in the clinical datasets (EG). It is better to keep the current version and upload the new ones as new version, so we could access both. If the new ones are complete replacements of the old ones, then the old ones could be removed after the new ones are available.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
08/11/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208434 **INFORMATION REQUEST**

Hoffmann-La Roche Inc.
Attention: Chez Min Murdoch, Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Mr Murdoch,

Please refer to your original New Drug Application received 208434 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alectinib capsule 150 mg strength.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response prior to COB Tuesday, September 08, 2015.

During a recent FDA inspection of (b) (4) drug substance manufacturing facility in (b) (4) for this NDA, our field investigator found that the Alectinib drug substance stability data submitted in the NDA filing was not generated by (b) (4) (b) (4). Provide the information about the facility(ies) for the registration stability testing of both Alectinib drug substance and drug product. Update the 356h form, and Sections 3.2.S.2.1 and 3.2.P.3.1 accordingly.

If you have any questions, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

Olen Stephens -S

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Olen Stephens, Ph.D.
Branch Chief, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208434 **INFORMATION REQUEST**

Hoffmann-La Roche Inc.
Attention: Chez Min Murdoch, Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Mr. Murdoch,

Please refer to your original New Drug Application received Thursday, July 16, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alectinib capsule, 150 mg.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response prior to COB Monday, August 31, 2015.

1. **An outstanding deficiency has been sent to the DMF (b) (4) holder regarding your NDA. Contact the DMF holder to assist the resolution of this deficiency.**

2. **We acknowledge that for batch # 6503100-1307040, 6503100-1307049, and 6503100-1307085, you have provided the executed manufacturing batch records and bulk package information; however, we couldn't locate the executed packaging record for these three batches. Please provide accordingly. Furthermore, since the batch records are written in (b) (4), please make sure to include the English translation for all section of the batch records.**

3. **We are in the process of reviewing your proposed dissolution method and dissolution acceptance criteria for alectinib oral capsules. Provide the *in vitro* dissolution data for the RO5424802/F07 capsules containing (b) (4)% SLS relative to alectinib (Batch Number 1134459, expires 31 July 2015) generated at time of manufacturing release and, if available, during long-term and accelerated stability testing.**

If you have any questions, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

Olen Stephens -S

Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Olen Stephens -S, 0.9.2342.19200300.100.1.1=2000558826
Date: 2015.08.10 13:48:53 -04'00'

Olen Stephens, Ph.D.
Branch Chief, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208434

METHODS VALIDATION
MATERIALS RECEIVED

Hoffmann-La Roche Inc.
Attention: Chez Min Murdoch
Regulatory Program Management
1 DNA Way
South San Francisco, CA 95080

Dear Chez Min Murdoch:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Alectinib capsules, 150 mg and to our July 28, 2015, letter requesting sample materials for methods validation testing.

We acknowledge receipt on August 6, 2015, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-2155), FAX (314-539-2113), or email (Laura.Pogue@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Laura C. Pogue, Ph.D.
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

LAURA POGUE
08/06/2015

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

Memorandum

Date: August 4, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434 Hoffmann-La Roche – alectninb(proposed proprietary name Alecensa) – FDA request for information - CMC

Dear Ms. Murdoch:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for "alectinib (proposed proprietary name Alecensa)."

Currently your application is under review and we have the following comments and requests for information.

1. Provide samples of the container closure system including the bottle and closures for both the [redacted] (b) (4) bottles.

2. Identify the location of the [redacted] (b) (4) bottles.

Please provide a response as soon as possible. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
08/04/2015

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

Memorandum

Date: August 3, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434 – Hoffmann-La Roche, Inc. – alectinib (proposed proprietary name Alecensa) - Application Orientation Meeting

---

Dear Ms. Murdoch,

You were contacted by The Division of Oncology Products 2 requesting that Hoffmann-La Roche, Inc. schedule an Application Orientation Meeting for the New Drug Application (NDA) for the product alectinib (proposed proprietary name Alecensa) for the treatment of ALK positive non-small cell lung cancer (NSCLC).

Your Application Orientation Meeting has been scheduled for August 10, 20125 from 2:00 PM – 3:00 PM (EST).

Please send me the names of all staff members that will be present at this presentation. I am including a foreign visitor form to be filled out by all non-US citizens. Please send this information to me by close of business Thursday, August 6, 2015.

I have also included a form that will assist your team with your presentation. We ask that your team consist of no more than 10 members. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, MT
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosures:
Foreign Visitor Form
OHOP General Advice and Application Orientation Presentation Meetings

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH **(MM/DD/YYYY)**	
PLACE OF BIRTH **(city and country)**	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL **(**name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

OHOP's General Advice for Application Orientation Presentation Meetings

Within 45 days after arrival of a new NDA, original BLA or efficacy supplement, FDA may hold an Application Orientation Presentation meeting with you for purposes of orienting the review team to the content and format of the application. Preferably, the meeting would take place as soon as possible once the application has been submitted so that the review team can become familiar with your application.

Below are comments, which are intended to help in your presentation preparation. This list is not inclusive of all issues that you should consider in preparing for your presentation, but highlights areas of interest to OHOP. These are general comments and we acknowledge that individual applications have unique characteristics. We also acknowledge that information needed to support a new NDA or original BLA will differ from an efficacy supplement. If you believe some comments are inapplicable to your application and therefore your presentation and/or you believe that other information is relevant, adjust your presentation accordingly.

Application Orientation Presentation meetings are generally one hour in length, including time for discussion and Q & A (approximately 35-40 minutes of presentation and 25-20 minutes for discussion). The primary focus of the presentation should be on clinical (with clinical sections presented first) with highlights of other sections to follow (i.e., 1-2 slides for remaining sections).

Administrative:

1. Sponsor attendees

2. Presentation outline or Agenda. Should list sections included in submission.

Background and Application Specifics:

3. Proposed indication(s) and current indication(s), if efficacy supplement. Dosing recommendation from proposed labeling.

4. Drug/biologic characteristics, including what makes the drug/biologic unique, mechanism of action.

5. Listing of registration trial(s), to support marketing/licensing application, as well as Phase 1 and Phase 2 trials to support application.

6. Statement of whether you plan to seek approval under 21 CFR 314.510, Subpart H/21 CFR 601.41, Subpart E (i.e., accelerated approval) or full approval. If accelerated approval, design of the confirmatory trial(s) that will be ongoing at the time of accelerated approval and a timetable of when confirmatory trial(s) will be completed and final clinical study report(s) submitted.

7. Regulatory history, including the following:
    - Orphan Drug designation, Fast Track designation
    - Foreign Regulatory history: Where/when approved and for what indications, whether there are pending applications with foreign regulators, Risk management plans in foreign countries.
    - Key Outcomes from FDA Interactions
        - EOP2 Meeting

- Special Protocol Assessment Correspondence: any agreements/disagreements on primary endpoints and key secondary endpoints, statistical analysis plan
- Pre-NDA/BLA meeting
- Other pertinent meetings/communications with FDA marking agreements/disagreements between you and the Agency

Summary Content of NDA/BLA/Efficacy Supplement Sections:

8. Clinical: Key findings from registration trials – Demographics of subjects and baseline characteristics, outcomes from primary and secondary endpoints, safety findings (most frequently reported adverse events, serious adverse events). Safety findings should also be presented from trials in other phases. NOTE: For demographics, you should address whether your study(s) represent ethnic minorities and whether study population is reflective of the U.S. population in which the drug/biologic is intended to be used.

   You should also present results of the following, as appropriate:
   - Clinical study sites (foreign or domestic)
   - Biomarker development for population selection (if applicable)
   - Assay validation (if applicable)

   120-day Safety update: Plans for 120-day Safety update, including how many additional patients will be included in safety update and from which studies.

9. Statistics: Study design, description of planned analyses, efficacy analyses, safety analyses, subpopulation analyses of safety and efficacy (age, sex, race, concurrent therapy, number of prior treatments, region/country), length of follow-up, handling of missing data

10. CMC: Manufacturing site locations and dates when available for inspection, brief summary of manufacturing process, comparability of drug substance and drug product after major manufacturing changes, characterization, controls, stability, status of drug master files, discuss any novel excipients, state if application is Quality by Design (ICH Q8, Q9, Q10)
    - For BLAs: Immunogenicity results, validated assay method, and manufacturing schedule for DS and DP.

11. Nonclinical: Brief summary of toxicology studies and findings, genetic toxicology, QT studies, effect on fertility or reproduction, carcinogenicity studies (if needed), qualification of drug impurities

12. Clinical Pharmacology: Exposure response relationship supporting dose selection, pharmacogenomics-related issues, Description/listing of PK studies, PK characteristics (metabolic pathway, metabolites, $t_{1/2}$, ADME, PK in special populations, drug-drug interactions).

13. If a Risk Evaluation and Mitigation Strategy (REMS) is included, you should briefly identify the risks to be addressed, list the goals of the REMS, and outline the REMS components (e.g. Medication Guide, Communication Plans and/or Elements to Assure Safe Use (ETASU).

14. Risk/benefit profile for drug/biologic

15. Summary

16. Q & A

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/s/

GINA M DAVIS
08/03/2015

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

Memorandum

Date: August 3, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434– Hoffmann-La Roche, Inc. – alectinib (proposed proprietary name Alecensa) – Data Listings - FDA request for information

---

Dear Ms. Murdoch:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for "alectinib (proposed proprietary name Alecensa)."

Currently your application is under review and we have the following comment and request for information.

> The site ID numbers for the data listings are different from the site ID numbers for the individual investigators for each study – Study NP28673 and Study NP28761. Please address this error immediately and submit the corrected information as a formal amendment to your NDA.

Please provide a response as soon as possible. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
08/03/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208434

REQUEST FOR METHODS VALIDATION MATERIALS

Hoffmann-La Roche Inc.
Attention: Chez Min Murdoch
Regulatory Program Management
1 DNA Way
South San Francisco, CA 95080

Dear Chez Min Murdoch:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Alectinib capsules, 150 mg.

We will be performing methods validation studies on Alectinib capsules, 150 mg, as described in NDA 208434.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

3.2.S.4.2.5	Assay and Determination of Related Substances in Alectinib HCl by HPLC
3.2.P.5.2.2	Identification of Alectinib Drug Product by HPLC
3.2.P.5.2.4	Identification, Content, and Degradation Products of Alectinib Drug Product by HPLC
3.2.P.5.2.5	Determination of (b) (4) in Alectinib Drug Product by GC-MS

Samples and Reference Standards

2 x 500 mg	Alectinib HCl reference standard
2 x 500 mg	Alectinib HCl drug substance
1 x 200 mg	Impurity (b) (4)
1 x 200 mg	Impurity (b) (4)
2 x 75 capsules	Alectinib (drug product)
3 ampules	(b) (4), analytical standard

Equipment

1	(b) (4)
1	

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-2155), FAX (314-539-2113), or email (Laura.Pogue@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Laura C. Pogue, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

LAURA POGUE
07/28/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208434

NDA ACKNOWLEDGMENT

Hoffmann-La Roche Incorporated
c/o Genentech, Inc.
Attention: Chez Min Murdoch
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Ms. Murdoch:

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

Name of Drug Product: Alectinib

Date of Application: July 6, 2015

Date of Receipt: July 6, 2015

Our Reference Number: NDA 208434

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 4, 2015, in accordance with 21 CFR 314.101(a).

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

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

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory

registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 208434** submitted on July 6, 2015, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

If you have any questions, call Gina Davis, Senior Regulatory Health Project Manager, at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Melanie Pierce
Acting Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

MELANIE B PIERCE
07/14/2015

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

Memorandum

Date: July 9, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 208434– Hoffmann-La Roche – alectinib – FDA request for information – OSI Inspections

---

Dear Ms. Murdoch:

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

Currently your application is under review and we have the following comment and request for information.

> In the Clinical Study Report for Study NP28761, the Study Summary Report on page 1806 of the CSR, listing number of patients screened and enrolled by site, is incomplete and contains errors. Please submit an updated and corrected version.

Please provide a response as soon as possible. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
07/09/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208434

ACKNOWLEDGE PRESUBMISSION

Hoffmann-La Roche, Incorporated
c/o Genentech, Incorporated
Attention: Chez Min Murdoch
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Ms. Murdoch:

We have received the first section of your New Drug Application (NDA) under the program for step-wise submission of sections of a marketing application under 506 of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Alecensa (alectinib), capsule 150 mg

Date of Submission: June 5, 2015

Date of Receipt: June 5, 2015

Our Reference Number: NDA 208434

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

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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

If you have any questions, call me at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Gina Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
06/25/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 111723

MEETING MINUTES

Hoffmann-La Roche, Inc.
Attention: Chez-Min Murdoch
Program Director, Regulatory Affairs
1 DNA Way MS
South San Francisco, CA 94080-4990

Dear Ms. Murdoch:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for alectinib.

We also refer to the meeting between representatives of your firm and the FDA on April 7, 2015. The purpose of the meeting was to review the results from Studies NP28761/AF-002JG and NP28673 and to reach agreement on the content and format of an NDA under the PDUFA V program, to support accelerated approval for the proposed indication of "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."

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

If you have any questions, call me at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosures:
Final Meeting Minutes
OSI pre-NDA/BLA Request
CMC Final Meeting Minutes
DOP 2 CDISC Guidance
Attendance Sheet

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING COMMENTS

Meeting Type:	B
Meeting Category:	pre-NDA
Meeting Date and Time:	April 7, 2015; 12:00 PM – 1:30 PM
Meeting Location:	CDER WO 22 - Room 1421
Application Number:	111723
Product Name:	alectinib
Indication:	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
Applicant Name:	Hoffmann-La Roche, Inc**.**

FDA ATTENDEES

Division of Oncology Products 2 (DOP 2)
Patricia Keegan, M.D., Director, DOP 2
Gideon Blumenthal, M.D., Medical Team Lead, DOP 2
Erin Larkins, M.D., Medical Officer, DOP 2
Gina Davis, M.T., Senior Regulatory Health Project Manager, DOP 2
Ruth Maduro, Regulatory Health Project Manager, DOP 2
Rebecca Cohen, R.N. Regulatory Health Project Manager, DOP 2

Division of Hematology Oncology Toxicology (DHOT)
Whitney Helms, Ph.D., Nonclinical Supervisor, DHOT
Sachia Khasar, Ph.D., Nonclinical Reviewer, DHOT

Division of Clinical Pharmacology (DCP V)
Stacy Shord, Pharm.D., Reviewer, DCP V

Division of Biostatistics V (DB V)
Shenghui Tang, PhD., Statistical Team Lead, DB V
Laura Fernandes, PhD., Statistical Reviewer, DB V

Division of New Drug Quality Assessment I, ONDP, OPQ
Olen Stephens, Ph.D., Acting Branch Chief

Division of Risk Management
Joyce Weaver, Pharm.D., Risk Management Analyst

SPONSOR ATTENDEES

Bogdana Ioana Balas, M.D. (Safety Science Leader)
Anna Beryozkina, PharmD. (Regulatory Program Manager)
Walter Bogdogna, PhD (Clinical Scientist)
Michael Budde (Associate Director Biostatistics)
Petra Buse (Biometrics Submission Team Leader)
Sarah Holland, D.Phil. Oxon, M.B.A. (Life Cycle Leader)
Mireille Methlin Costantzer, Pharm.D. (Global Regulatory Leader)
Annabelle Monnet (Project Lead Statistician)
Peter Morcos, PharmD (Clinical Pharmacology Lead)
Chez Min Murdoch (Regulatory Program Director)
Ali Zeaiter, M.D. (Global Development Leader)

BACKGROUND

On January 14, 2015, Roche submitted a meeting request to review the results from Studies NP28761/AF-002JG and NP28673 and to reach agreement on the content and format of an NDA under the PDUFA V program, to support accelerated approval (§CFR 314 Subpart H) for the proposed indication of "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."

Regulatory History

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

- On July 22, 2013, FDA held a Type B Post-Breakthrough Therapy designation-interdisciplinary meeting.

    - With regard to the clinical data package to support accelerated approval, FDA agreed that results from Studies NP28761 and NP28673, with safety information obtained in 250 patients treated at the recommended phase 2 dose (RP2D) and 70 patients from Study AF-001JP, could potentially permit a substantive review for accelerated approval. The clinical significance of the ORR and the adequacy of the data to support accelerated approval would consider the magnitude and duration the responses in a risk-benefit analysis at the time of review.
    - FDA agreed that the patient population, i.e., those with "crizotinib failure" defined as patients with prior treatment with crizotinib and progression based on RECIST criteria, version 1.1, with the last dose of crizotinib within 60 days of the first dose of study treatment was acceptable.
    - FDA noted that Roche's proposal to modify the protocol to target an overall response rate of 50% with the lower bound of 35% was acceptable. FDA stated that the results of the trial would be evaluated considering the safety profile of the drug and the durability of response.

- FDA stated that the results would need to demonstrate a substantial advance over available therapy to be considered for accelerated approval under subpart H.
- FDA generally agreed that verification of clinical benefit would be obtained in the randomized, active-controlled trial, Study BO28984.

- On November 14, 2013, a Type B meeting was held to discuss the acceptability of the design of Studies NP28761, NP28673 and BO28984 (b) (4)

  - FDA agreed (b) (4)
  - FDA noted that time to CNS progression in a single-arm study would not be interpretable.
  - FDA agreed to discuss the ability of CNS objective response rates (ORR) and durability of the responses in single-arm trials (b) (4) in a pre-NDA meeting.
  - Roche agreed to provide IRC-determined response rates and durations of response using both RECIST and RANO criteria. FDA acknowledged that investigator-determined response and progression will be based only on RECIST.

- On December 12, 2013, a Type B Pre-Phase 3 meeting was held with the FDA to discuss the design of the proposed confirmatory trial, Study BO28984, comparing the safety and efficacy of alectinib to crizotinib in the first-line treatment of ALK-positive NSCLC.

- On September 3, 2014, FDA issued an iPSP Agreement letter.

- On September 30, 2014, FDA provided preliminary feedback on the proposed content and format of the clinical section to support filing of the NDA. Roche stated their intent to submit NDA in June 2015. The clinical package for the proposed NDA would be primarily based on the analysis of results from Study NP28761 (data cutoff October 31, 2014, 85 patients in dose expansion cohort) and Study NP28673 (data cutoff August 18, 2014, 138 patients in dose expansion cohort), supported by data from Study AF-001JP.

  - FDA stated that the proposed clinical data package including data cut-off dates, as described, was acceptable.
  - FDA agreed with the proposed plans for submitting the patient narratives for all patients who died, dropped out or permanently discontinued study treatment, experienced serious adverse events, selected adverse events (ILD, $\geq$ Grade 3 hepatobiliary adverse events, and QTc prolongation), and any pregnancies for Studies NP28761, NP28673, and AF-001JP, was acceptable; FDA acknowledged that no on-study deaths occurred in Study AF-001J.
  - FDA agreed with the proposed plan to submit case report forms for all patients who died, dropped out or permanently discontinued study treatment, experienced serious

adverse events, selected adverse events (ILD, hepatobiliary adverse events ≥ Grade 3, and QTc prolongation), and any pregnancies for Studies NP28761 and NP28673.

- FDA agreed that Roche would not be required to submit case reports forms for the Study AF-001JP.
- FDA generally agreed with the content of the datasets provided in Appendices 1 through 3, of the pre-meeting package for the September 2014, meeting, provided that no substantial changes are made upon completion of programming for the primary analyses of Studies NP28761 and NP28673. FDA also agreed with the structure and format of the datasets for Studies NP28761, NP28673, and AF-001JP, but stated that this issue should be re-visited at the time of the formal pre-NDA meeting.
- FDA agreed with the plan not to provide radiographic images in the NDA and acknowledged Roche's commitment to make the images available upon request.
- While FDA agreed with the analysis plans for Studies NP28761 and NP28673, FDA noted that the adequacy of the data to support accelerated approval will consider the magnitude and duration the responses in a risk-benefit analysis during NDA review.
- FDA generally agreed with the proposed plan for integration of safety data in the Integrated Summary of Safety (ISS) and Summary of Clinical Safety (SCS). Roche agreed to provide a detailed justification for combining the safety data for Studies NP28761 and NP28673 in the SCS and to include tabulated summaries of key variables such as drug exposure and patients' baseline characteristics for each individual study and to summarize major differences between the design and conduct of the studies, including the eligibility criteria.
- Roche agreed to provide data on adverse events leading to study drug discontinuation, dose reduction, and dose delay/interruption as three distinct categories, such that FDA could distinguish whether an adverse event led to dose reduction or interruption in dosing.
- FDA agreed with the timing (90-day) and content (as proposed in the pre-meeting package) of the safety update

- On November 17, 2014, FDA provided preliminary feedback on the proposed non-clinical and clinical pharmacology strategy to support filing of the original NDA. The briefing package for the meeting contained a list of nonclinical studies, clinical pharmacology studies, and clinical studies to be submitted in the NDA to support the request for accelerated approval of alectinib for treatment of patients with ALK-positive, metastatic NSCLC that is resistant to crizotinib. The package also included summaries of the results of a food effect study, drug interaction studies with esomeprazole, posaconazole and rifampin and a mass balance and oral bioavailability study along with nonclinical data related to alectinib's drug metabolism and pharmacokinetics.

  - FDA agreed that, for NDA filing, the proposed plan to characterize the major cytochrome P450 enzymes that metabolize M4 and the human hepatic uptake of M4 via liver transporters and the rationale for not conducting additional CYP induction studies in human hepatocytes appeared reasonable.
  - FDA agreed that, for NDA filing, no further characterization of metabolite M1b was required, for filing of the NDA.

- FDA agreed that, for NDA filing, the 28-day rat toxicology study comparing alectinib with and without (b) (4)% SLS, was sufficient and no additional toxicology studies with SLS were required.
- Roche agreed to submit a QT study report along with the associated waveforms, datasets and text files in the NDA. FDA stated that Roche should also include a justification for not conducted a thorough QT study.
- Roche agreed to provide the results of their ongoing bioequivalence study in the NDA.
- FDA acknowledged Roche's plan to conduct the hepatic impairment study post-approval; Roche agreed to include the justification for how the safety of alectinib can be evaluated in the absence of this data along with the timelines for the conduct and completion of the proposed post-marketing study in the NDA.
- FDA agreed that, for NDA filing, Roche may submit their rationale for not conducting drug interaction studies with probe substrates of CYP2C8, BCRP and P-glycoprotein seems reasonable.
- Roche was advised to include the rationale for not conducted drug interactions studies in the NDA and to include the GastroPlus and Simcyp modelling and simulation reports, model files, datasets and other related files in the NDA to permit FDA to conduct an analysis.
- FDA agreed that, for NDA filing, submission of a renal impairment study was not required.
- FDA requested that Roche conduct and provide the results of formal analyses (e.g., multivariate logistic model, cox proportional hazard model, and case-control analysis) to further evaluate exposure-response relationship in the event of imbalance in prognostic factors across different categories of exposure.
- FDA advised Roche to ensure that the dose selection is robustly justified in the NDA.

- On January 27, 2015, FDA granted Orphan Drug Designation for the use of alectinib for the treatment of ALK-positive NSCLC.

- On March 19, 2015, a Pre-NDA Type B Meeting was held to discuss the content and format of the Quality information to be submitted in the proposed NDA.

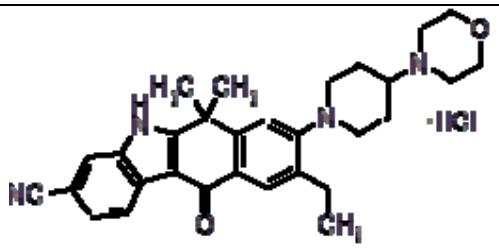
  - FDA agreed that ICHM7 LTL may be considered to calculate the permitted exposure level for Class (b) (4) and Class (b) (4) impurities and that the proposed control strategy for the (b) (4) compounds and for the (b) (4) appeared reasonable, however justification for control of these genotoxic impurities should be included in the NDA.
  - Roche agreed to provide a rationale and data to support a request for removing the requirement for (b) (4) testing in the NDA.
  - Roche agreed to provide data that demonstrates that the variability observed in (b) (4) properties resulting from the commercial process will not adversely impact product performance, specifically dissolution. Roche also agreed to provide specific information (as outlined in the meeting minutes) in the control strategy to be submitted in the proposed NDA.

- Roche agreed to provide data cited in the summary results presented at the meeting to support the proposed dissolution acceptance criteria of [(b) (4)]% at 30 minutes and Q=[(b) (4)]% at 75 minutes. Roche will also address FDA's concerns regarding the dissolution acceptance criteria, which are wider than recommended by FDA. Finally, Roche was advised to collect full dissolution profiles should be collected during the stability studies. FDA stated that the acceptability of the proposed dissolution acceptance criteria will be reviewed in light of full dissolution and manufacturing data at the time of NDA review.
- FDA agreed to Roche's proposal to provide 3 months accelerated and long-term site-specific stability data in the commercial packaging (250 mL round high-density polyethylene [HDPE] bottles with plastic child-resistant cap with integrated desiccant) would adequately support the use of a different container closure system and packaging site for the commercial product from that used for the primary registration batches.
- Roche agreed to provide a report regarding their investigation of the root cause for the observed differences in the dissolution profiles between drug products containing SLS from different sources in the NDA submission.

Description of Drug Product

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. This formulation was administered in Part 2 of Study NP28761 and in Study NP28673. The chemical name and structure of alectinib is provided in Table 1.

Table 1 Chemical Name and Structure of Alectinib

Structural Formula	
Chemical Name	9-Ethyl-6,6-dimethyl-8-[4-(morpholin-4-yl)piperidin-1-yl]-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile hydrochloride
Company Code	RO5424802-002
International Non-Proprietary Name	Alectinib (free base)[1]

1 The drug substance is alectinib hydrochloride, also referred to as alectinib HCl. All drug product dosage regimens and dosage strengths are expressed in terms of the free base.

The background package did not provide information regarding the proposed contents and format of the chemistry, manufacturing, and controls information to be included in the proposed NDA. This was preliminarily discussed at the March 19, 2015, meeting with FDA. FDA has provided additional comments on the content and format of this section of the NDA for discussion at this meeting.

Non-Clinical / Clinical Pharmacology

The background package did not provide information regarding the proposed contents and format of the non-clinical section and limited information on the clinical pharmacology section of the proposed NDA. This was preliminarily discussed at the November 17, 2014, meeting with FDA. FDA has provided additional comments on the content and format of these sections of the NDA for discussion at this meeting.

Clinical

The proposed NDA will contain the results of three clinical trials with the following clinical data cut-off dates:

- Study NP28761, clinical data cut-off date October 24, 2014
- Study NP28673, clinical data cut-off date August 18, 2014
- Study AF-001JP, clinical data cut-off date April 18, 2014

Studies NP28761 and NP28673 will be provide the primary efficacy and safety data in support of a request for accelerated approval.
Supportive safety and anti-tumor activity data will be provided from Study AF-001JP, conducted in Japanese patients with ALK-positive NSCLC who had not received prior crizotinib, in which patients received alectinib at doses ranging from 20 mg BID to 300 mg BID. The NDA will contain the clinical study report, safety and efficacy datasets, and narrative safety summaries for patients experiencing serious adverse events and adverse events of special interest, but no case report forms or financial disclosure information will be provided in the NDA.

Design and Key Results from the Major Efficacy Trials
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 include 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 ≤ 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.

In Part 1, there were two planned dose cohorts [600 mg orally, twice daily (BID) and 900 mg orally BID]; however Part 1 was terminated after enrollment of six patients in the 600 mg BID dose cohort based on external information (RP2D was confirmed to be 600 mg BID in Study NP28761). Patients in Part 2 received alectinib 600 mg BID. Upon disease progression, patients were offered to continue to receive alectinib in Part 3. In Part 3, patients whose pre-treatment tumor was EGFR negative or EGFR unknown were offered alectinib 600 mg BID while those with pre-treatment tumor harboring EGFR exon 19 deletions or exon 21 L858R substitution mutations were offered alectinib 600 mg BID and erlotinib 100 mg daily, at the discretion of their treating physician.
The co-primary objective of Part 2 were the objective response rate (ORR) per RECIST v1.1 as assessed by independent radiological review committee (IRC) and ORR as per IRC in subset of patients with prior exposure to cytotoxic chemotherapy. Secondary endpoints include ORR as per IRC using RECIST v1.1 in the subgroup of patients without prior exposure to cytotoxic chemotherapy, ORR per investigator review using RECIST v1.1, duration of response (DOR), central nervous system (CNS) objective response rate (CORR), CNS duration of response (CDOR), CNS progression rate (CPR) at 3, 6, 9, and 12 months, and characterization of the adverse event profile.

The planned sample size was 130 patients, which was chosen to ensure sufficient power in the subgroup of patients who were treated with prior chemotherapy, assuming a sample size of 85 patients, to reject the null hypothesis that ORR was ≤ 35%. A maximum of 45 chemotherapy-naïve patients were to be enrolled to ensure that 85 patients who received prior chemotherapy were enrolled.

As stated in the pre-meeting package, “given that Part 1 patients were merged into Part 2 and that the alectinib treatment period spanned Part 2 and Part 3, for the purposes of reporting the primary analysis and describing the endpoints, all parts of this study are considered as the Phase II portion.” Across Parts 1, 2, and 3, all patients received alectinib 600 mg BID orally within 30

minutes after meals in the morning and evening; alectinib was supplied as a 150 mg capsule formulation containing (b)(4)% SLS.

Results

Study NP28671
As of October 24, 2014, 134 patients (47 patients in Part 1 and 87 patients in Part 2) were enrolled in Study NP28671, with a median follow-up of 20.7 weeks (range: 4.6 – 59.4 weeks). Genentech states that 31 (36%) patients enrolled in Part 2, discontinued alectinib of whom 12 have died.

The primary efficacy population contains 69 patients; the primary efficacy population excludes 18 (21%) patients enrolled in Part 2 of Study NP28671, based on absence of measurable disease at baseline as determined by the IRC. Both the safety population and the efficacy populations used for secondary endpoints based on the investigator-assessment include all 87 patients enrolled in Part 2 Study NP28761.

Demographic information is provided for the safety population (n=78) but not for the primary efficacy population. In the safety population, the median age was 54 years, with 16 patients (18%) age 65 years or older, 84% were White and 8% were Asian, 55% had an ECOG PS of 1, 100% had received prior crizotinib, 96.6% had metastatic disease, and 94.3% had adenocarcinoma.

Study NP28673
As of August 18, 2014, a total of 138 patients were enrolled in Study NP28673, with a median follow-up is 30.3 weeks (range: 2.4 to 53.0 weeks). Genentech states that 35% of patients (n=49) have discontinued alectinib; the most common reason for discontinuation of alectinib was disease progression; 22% (11/49) of patients who discontinued treatment did so for adverse events. Twenty-four (17%) of those enrolled have died, 20 patient deaths were attributed to disease progression and four patients (3%) had fatal adverse events, consisting of intestinal perforation, dyspnea, pulmonary embolism, and hemorrhage.

The primary efficacy population contains 122 patients; the primary efficacy population excludes 16 (12%) patients based on absence of measurable disease at baseline as determined by the IRC. Both the safety population and the efficacy populations used for secondary endpoints based on the investigator-assessment include all 138 patients enrolled in Study NP28763.

Demographic information is provided for the safety population (n=138) but not for the primary efficacy population. In the safety population, 67% were White and 26% were Asian, 59% had an ECOG PS of 1, 100% had received prior crizotinib, 98.6% had metastatic disease, and 96.4% had adenocarcinoma.

Summary results for efficacy in Studies NP28761 and NP28673 are presented in the following table.

Populations/Efficacy Parameter	Study NP28673	Study NP28961
Modified intent-to-treat population[1]	n=138	n=87[2]
Evaluable for ORR by IRC	n=122	n=69
ORR	44%	48%
95% CI	(35%, 53%)	(36%, 60%)
Duration of response	9.2 mos	7.5 mos
Range (in months)	1.7+ – 9.2+	-
Evaluable for CORR	n=34	n=16
CORR (per RECIST)	56%	69%
95% CI	(39%, 73%)	(46%, 92%)

[1] all patients enrolled Study NP28673
[2] all patients enrolled in Part 2 of Study NP28671

The efficacy results of Study NP28761 and Study NP28673 will be presented separately in the NDA. In addition, Roche plans to pool data from Studies NP28761 and NP28673 in their analysis of CORR and to provide the CORR from each individual study.

OBJECTIVE

- To review 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.

SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSES

1. Does the Agency agree that the results from the pivotal Phase I/II trials NP28761 and NP28673 and supporting studies proposed to be included in this NDA, provide sufficient clinical evidence to characterize the benefit and risks of alectinib in patients with ALK-positive locally advanced or metastatic NSCLC who have progressed on or are intolerant to crizotinib, for accelerated approval?

   FDA response: FDA agrees that the study results proposed for inclusion in an NDA submitted under the provisions of 21 CFR 314 Subpart H (accelerated approval) may provide sufficient clinical evidence to characterize the benefit and risks of alectinib in patients with ALK-positive metastatic NSCLC who have progressed on crizotinib. However, the adequacy of the data will be determined during the review of the NDA.

   The study results are unlikely to provide sufficient clinical evidence to characterize the benefit and risks of alectinib in patients with locally advanced ALK-positive NSCLC, as only 5 patients across the two studies did not have metastatic disease (3 patients with stage IIIB, 2 patients with loco-regional recurrence).

Roche's April 6, 2015, electronic (email) communication to FDA's preliminary response to questions #1: The Sponsor would like to clarify that the patients with locally advanced disease proposed to be included in the indication are those that are not amenable to curative therapy, in line with the protocol inclusion criteria for both pivotal Phase I/II Studies (i.e. unresectable and not candidate for chemo-radiation treatment). Although the disease is not metastatic, these patients are treated in the same way as those with metastatic disease (Stage IV), as per NCCN guidelines. Therefore including patients with locally advanced disease not amenable to curative therapy in the indication would be consistent with the guidelines for treatment of this disease.

Discussion during the meeting: FDA acknowledged Roche's response and stated that the indication will be determined based on review of the NDA.

2. Does the Agency agree that results from the pivotal Phase I/II trials NP28761 (N= 134) and NP28673 (N= 138) provide sufficient evidence to characterize the benefit and risks of alectinib in the 150 mg hard capsule formulation containing (b)(4)% SLS and support the NDA submission?

FDA response: FDA agrees that the study results from Studies NP28761 and NP28673, which include efficacy data obtained in 191 patients (69 and 122 patients, respectively) evaluated for ORR and DOR by the IRC and the safety experience in 272 patients (134 and 138 patients, respectively) who received, may provide sufficient evidence to characterize the risks of alectinib in the 150 mg hard capsule formulation containing (b)(4)% SLS and support the filing of the proposed NDA. However, the adequacy of the data to support approval or specific claims will be determined during the review of the NDA.

Discussion during the meeting: Roche acknowledged FDA's preliminary response to question #2 and no discussion occurred.

3. Based on the NP28673 and NP28761 studies, the Sponsor proposes the following indication:

> "Alectinib is indicated for the treatment of patients with ALK-positive, locally advanced or metastatic NSCLC who have progressed on or are intolerant to crizotinib."

This indication statement will be supported by the data in the patient population in the NP28673 (N= 138) and NP28761 (N= 134) studies. Does the Agency agree with this proposal?

FDA response: No, FDA does not agree; see the FDA Response to Question 1. In addition, please note that the indication statement will be determined during the NDA review.

Discussion during the meeting: Roche acknowledged FDA's preliminary response to question #3 and no discussion occurred.

4. Given the consistent efficacy observed in the CNS in both pivotal Studies NP28673 and NP28761, does the Agency agree with the Sponsor's proposal to include the protocol-defined CNS secondary efficacy endpoints CORR and DCR, and CDOR for pivotal Studies NP28673 and NP28761 in Section 14.1 Clinical Trials of the USPI? The Sponsor proposes to present pooled CORR and DCR, and CDOR.

FDA response: The adequacy of the data to support the inclusion of these secondary efficacy endpoints in the USPI will be determined during the review of the NDA. The secondary endpoint of disease control rate is unlikely to be included in product labeling.

Roche's April 6, 2015, electronic (email) communication to FDA's preliminary response to question #4: The Sponsor would like clarification on the FDA's rationale as to why the secondary endpoint CNS DCR is unlikely to be included in the product labelling. In addition to patients that achieved a CR or PR, DCR also describes the benefit in patients that had their CNS disease stabilized (SD).

CNS disease is associated with significant morbidity due to both the brain involvement and the treatment required to control the disease (including corticosteroids, surgery, and radiation). Therefore, the Sponsor considers the ability to at least stabilize CNS disease and related symptoms to be clinically meaningful for physicians.

Alternatively, the Sponsor would like to propose the inclusion of Complete Responses (CRs) in patients with measurable and/or non-measurable CNS lesions at baseline. In clinical practice, measurability of CNS disease according to RECIST is not considered in the treatment decision for these patients with high unmet medical need. Patients with non-measurable CNS lesions at baseline cannot achieve Partial Responses (PRs), i.e. can only achieve CRs, and thus the Sponsor considers this to be clinically meaningful information for physicians.

Discussion during the meeting: FDA stated that DCR is not a measure of clinical benefit as the treatment effect cannot be discerned in a single arm study trial as compared to the natural history of CNS metastases in ALK-positive NSCLC. FDA further stated that it is unclear how DCR leads to patient benefit, in contrast to partial or complete responses where reduction in tumor size may be linked to a reduction in tumor-related symptoms. Roche acknowledged FDA's response.

Roche proposed that language be included in product labeling describing the complete response rate in the CNS, as confirmed by the IRC, in patients with measurable or non-measurable CNS metastases based on a pre-specified exploratory analysis of pooled data from both Study NP28673 and Study NP28761. FDA agreed to evaluate the proposed language and data supporting this language.

5. Given that the DOR and CDOR from the Primary Analysis of NP28673 (18 August 2014) and the DOR and CDOR from the Primary Analysis of NP28761 (24 October 2014) are not yet mature. Does the Agency agree with the proposal for

additional efficacy data cuts and the format in which the data will be presented?
FDA response: No. The application should be complete at the time of the NDA submission. Only minor components may be submitted within 30 days following submission of an NDA (or the final component of a rolling NDA). Therefore, FDA cannot commit to reviewing updated DOR and CDOR from Study NP28761.

Roche's April 6, 2015, electronic (email) communication to FDA's preliminary response to question #5: The Sponsor acknowledges the FDA's feedback and proposes to include the NP28673 January 8, 2015 follow-up data cut as assessed by IRC based on RECIST, in the NDA, and has summarized the data below as it has become available since submission of the Pre-Meeting Package (PMP).

	NP28673 Primary Analysis August 18, 2014 n=138	NP28673 Follow-Up Data Cut January 8, 2015 n=138
Primary Endpoint by IRC (n) ORR [95% CI]	60 / 122 49.2% [40.0 ; 58.4]	61 / 122 50.0% [40.8 ; 59.1]
DOR (n) Patients with events median in months [95% CI]	60 12 (20%) 9.2 [NE]	61 20 (32.8%) 11.2 [9.6 ; NE]
PFS by IRC Patients with events median in months [95% CI]	 61 (44.2%) 7.5 [5.9;11.2]	 80 (58.0%) 8.9 [5.6 ; 11.3]
CNS ORR (measurable) Patients with events ORR [95% CI] CR	34 19 55.9% [37.9 ; 72.8] 5 (14.7%)	35 20 57.1% [39.4 ; 73.7] 7 (20.0%)
CNS ORR (measurable & non measurable) Patients with events ORR [95% CI] CR	83 32 38.6% [28.1 ; 49.9] 18 (21.7%)	84 36 42.9% [32.1 ; 54.1] 23 (27.4%)
CNS DOR (measurable) Patients with events median in months [95% CI]	19 4 (21.1%) 7.6 [5.8 ; 7.6]	20 11 (55.0%) 9.1[5.8 ; NE]
CNS DOR (measurable & non measurable) Patients with events median in months [95% CI]	32 7 (21.9%) 7.6 [5.5 ; 10.3]	36 18 (50.0%) 10.3 [7.6 ; 11.2]

The Sponsor agrees to only include safety data in the Day 90 Safety Update Report as per standard.

Discussion during the meeting: FDA acknowledged Roche's response and stated that use of the new data cut-off date of January 8, 2015, for efficacy results from Study NP28673, is acceptable. Roche stated that this would provide an additional four months of follow-up for these efficacy results.

6. Given the unmet medical need in patients with ALK-positive locally advanced or metastatic NSCLC population who have progressed on or are intolerant to crizotinib, the magnitude of treatment effect and the favorable safety and tolerability profile of alectinib observed in Studies NP28673 and NP28761, does the Agency agree that this represents a sufficient advancement in the treatment of this patient population to qualify the proposed NDA for Priority Review?

   FDA response: FDA makes the determination of the review designation following receipt of the NDA submission and in the context of available therapy at the time of that submission.

   Discussion during the meeting: Roche acknowledged FDA's preliminary response to question #6 and no discussion occurred.

7. In light of the results from Studies NP28673 and NP28761, does the Agency agree with the proposal to not submit a REMS or a Medication Guide for the use of alectinib in the proposed indication?

   FDA response: At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of alectinib outweigh the risks, and if it is necessary, what the required REMS elements will be. The need for a REMS will be determined during the review of the application.

   FDA agrees that the NDA submission does not need to include a REMS proposal in order to be filed.

   Discussion during the meeting: Roche acknowledged FDA's preliminary response to question #7 and no discussion occurred.

8. Does the Agency foresee that the proposed NDA will be reviewed by the ODAC?

   FDA response: FDA cannot comment as determination of the need for advice from the ODAC is made after NDA submission.

   Discussion during the meeting: Roche acknowledged FDA's preliminary response to question #8 and no discussion occurred.

9. Would the Agency like to have an orientation meeting with the Sponsor after the submission of the NDA to outline the major components of the NDA?

   FDA response: Yes.

   Roche's April 6, 2015, electronic (email) communication to FDA's preliminary response to question #9: The Sponsor proposes the week beginning August 3, 2015 for the Applicant Orientation Meeting and Technical Walkthrough.

Discussion during the meeting: FDA will evaluate schedules and provide feedback on whether or not the proposed date for the Application Orientation meeting is feasible.

10. Would the Agency accept a rolling review with earlier submission of Module 4 and the Module 5 CSRs of Clinical Pharmacology and Phase I/II Studies in June 2015 for the planned submission of the NDA in July 2015?

FDA response: FDA agrees to Roche's proposal to submit Module 4 and the clinical study reports (CSRs) for the Clinical Pharmacology Studies NP28991, NP28989, NP28990, NP29040 and NP29042, and Studies NP28673, NP28761 and AF-001JP to Module in June 2015. It is FDA's understanding that all other components of the complete application will be provided in a single submission in July 2015.

Roche's April 6, 2015, electronic (email) communication to FDA's preliminary response to question #10: The Sponsor would like to clarify that the clinical study reports (CSRs) for the Clinical Pharmacology Studies NP28991, NP28989, NP28990, NP29040 and NP29042, and Studies NP28673, NP28761 and AF-001JP will include the data sets, annotated CRFs, define files and reviewer guide.

Discussion during the meeting: Roche clarified that the NDA will be submitted as 3 components:

- The first component to be submitted in early June 2015 to include most of Module 1 (except the Risk Management Plan and the proposed US package insert) and most of Module 4.
- The second component, to be submitted in mid to late June 2015, will include the CSRs, datasets, annotated CRFs, define files and reviewer guide, as well as most of the data requested by FDA Office of Scientific Investigations.
- The final component to be submitted by July 6, 2015, will include population pharmacokinetic (PK) analysis, the PBPK analysis, all of Module 2, and the integrated clinical data sets, and any outstanding items from Module 1 (unless submitted earlier).

The timing for submission of the CMC information has not yet been determined and will be conveyed prior to June 1, 2015.

11. Does the Agency agree with the proposed content, structure and format of the data sets for the pivotal Studies NP28673 and NP28761, supporting Japanese Study AF-001JP (Chugai sponsored) and Clinical Pharmacology Studies NP29042, NP28989, NP28990, NP28991 and NP29040?

FDA response: Yes, FDA agrees with the proposed content, structure and format of the datasets for Studies NP29042, NP28989, NP28990, NP28991 and NP29040. See FDA's Additional Comments 13, 14 and 15 for recommendations relating to the submission of the clinical datasets and clinical pharmacology data.

In addition, as discussed at the meeting between Roche and FDA on November 17, 2014, include the following information in the original NDA submission;

a. Study reports for the pooled QT/QTc interval assessment, the population pharmacokinetic analysis, and exposure-response analysis.

b. Justification for how the safety of alectinib can be evaluated in the absence of data in patients with hepatic impairment as it relates to proposed labeling. Provide timelines for the conduct and completion of the proposed post-marketing study in patients with hepatic impairment.

c. Justification for not conducting a study in patients with renal impairment.

d. Justification for not conducting a drug interaction study with appropriate P-glycoprotein, BCRP and CYP2C8 probe substrates. Include the modelling and simulation reports, model files, datasets and other related files to support justification (see additional comment 14i).

e. In vitro studies characterizing the ability of alectinib to be a substrate, inhibitor and inducer of the major cytochrome P450 enzymes and of alectinib to be substrate and inhibitor of multiple transporters. Include the mechanistic static model used to estimate the AUC ratios for alectinib with CYP3A4 and CYP2C8 substrates.

f. In vitro studies characterizing the ability of M4 to be a substrate and inhibitor of the major cytochrome P450 enzymes and multiple transporters and characterize the hepatic uptake of M4.

g. Modeling and simulations to determine the interaction with a strong CYP3A4 inhibitor and a strong CYP3A4 inducer after multiple dosing of alectinib (see additional comment 14i).

FDA also refers to the September 30, 2014 Type C meeting regarding preliminary expectations for the content and format of the clinical safety and efficacy data. As discussed at that meeting, you agreed to include the following information in the NDA submission:

- Case report forms (CRFs) and narratives for patients who died, dropped out or permanently discontinued study treatment, experienced serious adverse events, experienced selected adverse events of interest (i.e., interstitial lung disease, grade ≥3 hepatobiliary adverse events, and QTc prolongation), or became or were pregnant during for Studies NP28673 and NP28761.

- Ensure that the integrated safety dataset for Studies NP28673 and NP28761 contains a study identifying variable to allow analysis of the data for each individual study.

- Identification of, and data for, all adverse events leading to discontinuation, leading to dose reduction, or leading to dose delay/interruption will be presented in the NDA individually (i.e., not as an aggregate). In addition, median time to first dose reduction or delay/interruption and median duration of dose delay/interruption will also be presented.
  Discussion during the meeting: Roche acknowledged FDA's preliminary response to question #11 and no discussion occurred.

12. Does the Agency agree that Financial Disclosures are only required for pivotal Studies NP28673 and NP28761, and that Financial Disclosures are not required forsupporting Japanese Study AF-001JP?

    FDA response: Yes, FDA agrees.

    Discussion during the meeting: Roche acknowledged FDA's preliminary response to question #12 and no discussion occurred.

Additional Comments

Clinical

13. In the original NDA submission, provide the following additional information in the NDA from Studies NP28673 and NP28761 in the study datasets and summarize the results in the clinical study reports for each study:

    - The number of patients who stopped crizotinib therapy due to progressive disease and number of patients who stopped crizotinib therapy due to intolerance.

    - The interval between the last dose of crizotinib and the start of treatment with alectinib.

    - A study variable/flag for each patient in all integrated datasets, including the dataset for the pooled analysis of CORR from Studies NP28673 and NP28761.

    Discussion during the meeting: Roche acknowledged FDA's Additional Comment #13 and no discussion occurred.

Clinical Pharmacology

14. Address the following clinical pharmacology related questions in the clinical pharmacology summary in the NDA submission.

    a. What is the basis for selecting the dose and regimen used in the registration trials?

    b. What are the exposure-response relationships for activity and safety?

c. How was the potential to prolong the QT interval assessed? What are the conclusions and proposed labeling?

d. What are the characteristics of absorption, distribution, and elimination?

e. What are the effects of food on the bioavailability? What are the dosing recommendations with regard to meals or meal types? Provide justification for the recommendation with regard to meals or meal types.

f. What influence do intrinsic factors (such as sex, race, weight, disease, hepatic impairment, renal impairment) have on exposure, activity and safety? What dose modifications are recommended for each factor?

g. What influence do the extrinsic factors (such as concomitant medications or drug interactions) have on exposure, activity and safety? What dose modifications are recommended for these factors?

Discussion during the meeting: Roche acknowledged FDA's Additional Comment #14 and no discussion occurred.

15. Apply the following advice in preparing clinical pharmacology sections of the original NDA submission.

a. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics studies.

b. Provide complete datasets for clinical pharmacology and biopharmaceutics studies. The subject's unique ID number in the PK datasets should be consistent to those in datasets submitted for clinical review.

c. Provide all concentration-time and derived PK parameter datasets as SAS transport files (xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

d. Present PK parameter for alectinib, M4 and the composite as geometric mean with coefficient of variation, mean ± standard deviation or median with range, as appropriate, in each study report.

e. Identify individual subjects that required a dose reduction, interruption or discontinuation; the time to the first dose reduction, interruption or discontinuation; the reasons for dose reduction, interruption or discontinuation within the population pharmacokinetic and exposure-response datasets. Provide the appropriate descriptive statistics for each of these variables in support of the proposed dose and regimen.

f. Submit the following information and data for the population pharmacokinetic analysis:

- SAS transport files (xpt) for all datasets used for model development and validation.
- Description of each data item provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
- Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submit these files as ASCII text files with txt extension.
- Model development decision tree or table which gives an overview of modeling steps.
- Include the following in the population PK report

    - Standard model diagnostic plots
    - Individual plots for a representative number of subjects including observed concentrations, the individual prediction line and the population prediction line
    - Model parameter names and units in tables. For example, apparent oral clearance should be presented as CL/F (L/h) and not as THETA(1).
    - Summary of the report describing the clinical application of modeling results.

Refer to the following pharmacometric data and models submission guidelines http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm for more information.

g. Submit exploratory exposure-response analyses for safety and activity for alectinib and M4 in NSCLC. Refer to Guidance for Industry found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf and http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for more information.

h. Submit a pooled QT/QTc interval assessment and include the following items.

- Copy of the protocols that included ECG monitoring
- Copy of the Investigator's Brochure
- Annotated CRF
- Define file which describes the contents of the electronic data sets

- Electronic data sets as SAS transport files (in CDISC SDTM format – if possible) and all the SAS codes for the analyses
- ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
- Completed Highlights of Clinical Pharmacology Table

i. PBPK reports should include the purpose of the simulations, assumptions being made, detailed process of PBPK model building and verification, a summary of model input parameters, software version, and simulation results and conclusions. Provide the study report as PDF files. Include the model files used to generate the final PBPK simulations. These files should be executable by the FDA reviewers using the specified software. Include appropriate supporting documentations such as any special instructions and file definitions.

Discussion during the meeting: Roche acknowledged FDA's Additional Comment #15 and no discussion occurred.

Non-clinical Pharmacology/Toxicology

16. Please confirm that the proposed content and format of the non-clinical pharmacology and toxicology sections of the proposed NDA are consistent with the proposals in the premeeting package for, and the discussion during, the November 17, 2014, meeting with FDA.

Discussion during the meeting: Roche acknowledged FDA's Additional Comment #16 and no discussion occurred.

Chemistry and Manufacturing Controls

17. As soon as possible, preferably at the preNDA meeting, provide a list of the proposed testing and manufacturing sites to be included in the NDA. For each site, state whether these sites have an inspectional history with the FDA and if so, whether there are any known pending site specific issues at this time.

Discussion during the meeting: Roche acknowledged FDA's Additional Comment #17 and no discussion occurred.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

In addition, we note that a chemistry/multidiscipline pre-submission meeting was held on March 19, 2015. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

SUMMARIZE DISCUSSION AND AGREEMENTS

- The content of a complete application was discussed, based on the meeting briefing packages for the respective meeting, on September 30, 2014 and April 7, 2015, with regarding to the clinical sections; November 17, 2014 and April 7, 2015, with regard to the non-clinical pharmacology and clinical pharmacology sections; and on March 19, and April 7, 2015, with regard to the chemistry, manufacturing, and controls section. In addition, discussion of the requirement for a REMS to support filing of the proposed NDA was discussed during the April 7, 2015, meeting. Agreement was reached on the content of the application. Roche agreed to submit a complete application in three components.

    - The first component in early June 2015 to include most of Module 1 (excludes RMP and USPI) and most of Module 4.

    - The second component, to be submitted in mid to late June 2015, to include the CSR, data sets, annotated CRFs, define files and reviewer guide, as well as OSI data request.

    - The final component, to be submitted by July 6, 2015, to include population PK analysis, PBPK, all of Module 2, and the integrated clinical data sets.

    - The timing for submission of the CMC information has not yet been determined and will be conveyed prior to June 1, 2015.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application. Roche confirmed that they will provide this information in the NDA. Roche agreed to provide a list of the proposed testing and manufacturing sites to be included in the NDA. In addition, for each testing or manufacturing site, Roche will state whether these sites have an inspectional history with the FDA and if so, whether there are any known pending site specific issues at this time. If available, prior to submission of the NDA, Roche may submit this information to the IND.

- A preliminary discussion on the need for a REMS was held and it was concluded that a REMS would not be required for filing of the proposed NDA. (see Discussion During Meeting regarding Question 7). A final determination of the requirement for a REMS to ensure safe and effective use will be made during review of the NDA. FDA will notify Roche during the review, if it is determined that a REMs will be necessary.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. Roche stated its intent to submit a complete application and therefore there are no agreements for late submission of application components.

PREA REQUIREMENTS

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

Because none of the criteria apply at this time to your application, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

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

MANUFACTURING FACILITIES

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

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for CGMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Office of Scientific Investigations (OSI) Requests

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

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

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

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

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

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

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

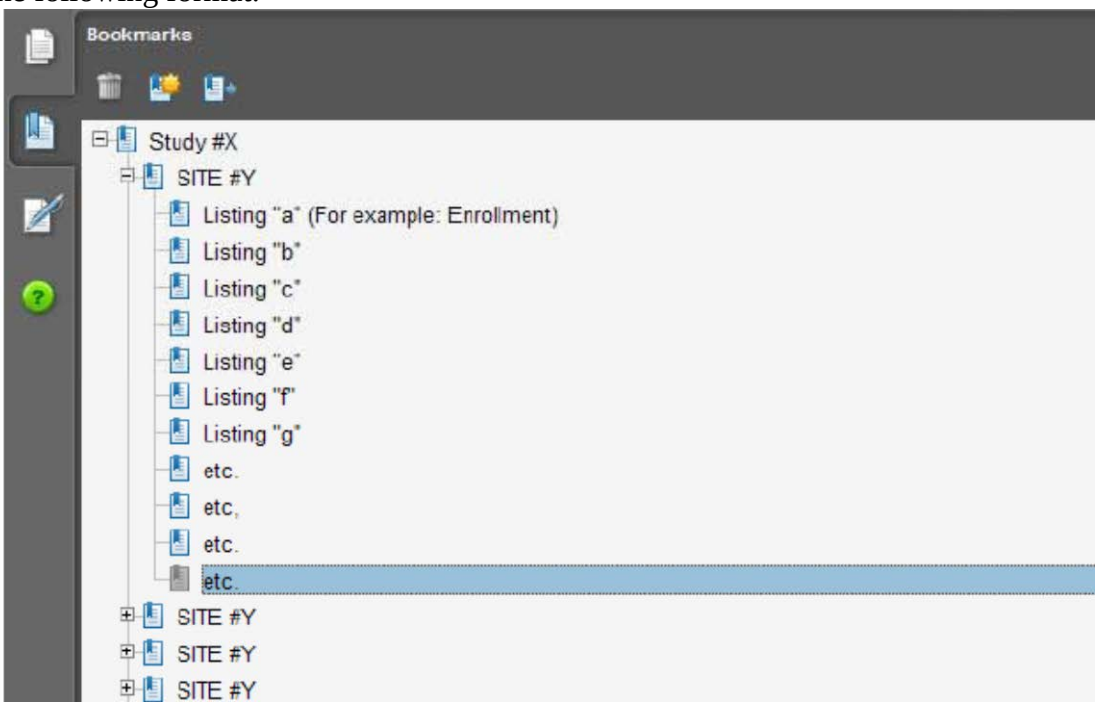
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:

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

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



III. Request for Site Level Dataset:

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

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

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

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

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

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

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

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

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

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

APPENDIX I

Additional DOP2 CDISC Guidance

The following two tables identify variables and domains that the division uses in conducting standardized analyses on data for marketing or licensing applications. Following the tables is a description of the Tumor Identification (TU), Tumor Results (TR), Response (RS), domains and variables therein. These are provided because DOP2 uses these domains and variables in analysis tools developed by FDA. These domains and variables will be added to the CDISC implementation guide in the near future, however, we request that you implement the use of this STDM format with all your upcoming submissions.

Please use the draft CDISC *Oncology Disease-Specific Therapeutic Area Supplement to the SDTM Implementation Guide* (http://www.cdisc.org/sdtm) for submitting tumor identification, results, and response data to DOP2 as soon as they become available.

Please follow the guidance as provided in the CDER Data Standards Issues Document that can be found at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

Table 1: Variables that DOP2 requires for analyses of OS, PFS, RR, Disposition, and Adverse Reactions

Domain	Variable Name	Variable Label	Required Variable Values	Currently Available	CDISC Core	CDISC Data Type	CDISC Code List
ADSL	STRATA<N>	Based on definition of strata variable	0,1	No		Num	0,1
AE	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
AE	AEBODSYS	Body System or Organ Class	--	Yes	Exp	Char	
AE	AEDECOD	Dictionary-Derived Term	--	Yes	Req	Char	
AE	AETOXGR	Standard Toxicity Grade	--	Yes	Perm	Char	
AE	AESTDTC	Start Date/Time of Adverse Event	--	Yes	Exp	Char	ISO 8601
CM	CMCAT	Category for Medication	ANTI-CANCER	Yes	Perm	Char	--

CM	CMDECOD	Standardized Disposition Term	--	Yes	Perm	Char	NCOMPLT (Completion/Reason for Non-Completion)
CM	CMENDTC	End Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDY	Study Day of Start of Medication	--	Yes	Perm	Num	--
CM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DM	AGE	Age	--	Yes	Req	Num	--
DM	AGEU	Age Units	--	Yes	Exp	Char	AGEU
DM	ARM	Description of Planned Arm	--	Yes	Req	Char	--
DM	ACTARM		--	New			--
DM	ARMCD	Planned Arm Code	--	Yes	Req	Char	--
DM	COUNTRY	Country	--	Yes	Req	Char	ISO 3166 3- char. code
DM	DTHDTC	Date of Death	--	New		Char	ISO 8601
DM	DTHFL	Subject Death Flag	Y	New		Char	--
DM	ETHNIC	Ethnicity	--	Yes	Perm	Char	--
DM	RACE	Race	--	Yes	Exp	Char	--
DM	RFPENDTC	Date/Time of End of Participation	--	New		Char	ISO 8601
DM	SEX	Sex	--	Yes	Req	Char	M, F, U
DM	SITEID	Study Site Identifier	--	Yes	Req	Char	--
DM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DS	DSCAT	Category for Disposition Event	PROTOCOL MILESTONE	Yes	Perm	Char	DSCAT
DS	DSDECOD	Standardized Disposition Term	DEATH, RANDOMIZED, LOST TO FOLLOW-UP, ALIVE,ADVERSE EVENT, PROGRESSIVE DISEASE	Yes	Req	Char	NCOMPLT (Completion/Reason for Non-Completion)

DS	DSDTC	Date/Time of Collection	--	Yes	Perm	Char	ISO 8601
DS	DSSCAT	Subcategory for Disposition Event	STUDY DISCONTINUATION, TREATMENT DISCONTINUATION, STUDY TERMINATION	Yes	Perm	Char	--
DS	DSSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
DS	DSSTDY	Study Day of Start of Disposition Event	--	Yes	Perm	Num	--
DS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	EXSTDTC	Start Date/Time of Treatment	--	Yes	Exp	Char	ISO 8601
EX	EXENDTC	End Date/Time of Treatment	--	Yes	Perm	Char	ISO 8601
LB	LBBLFL	Baseline Flag	Y	Yes	Exp	Char	NY
LB	LBNRIND	Reference Range Indicator	HIGH, LOW	Yes	Exp	Char	--
LB	LBTEST	Lab Test or Examination Name	--	Yes	Req	Char	--
LB	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
MH	MHDECOD	Dictionary-Derived Term	--	Yes	Perm	Char	--
MH	MHENDTC	End Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601
MH	MHSTDTC	Start Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601
MH	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	RSACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null

RS	RSDTC	Date/Time of Response Assessment	--	Yes	Exp	Char	ISO 8601
RS	RSEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
RS	RSSTAT	Response Assessment Status	NOT DONE	Yes	Perm	Char	ND
RS	RSSTRESC	Response Assessment Result in Std Format	CR or COMPLETE RESPONSE, PR or PARTIAL RESPONSE, SD or STABLE DISEASE, PD or PROGRESSIVE DISEASE, NE or NOT EVALUABLE	Yes	Exp	Char	--
RS	RSTESTCD	Response Assessment Short Name	OVRLRESP, looks for TGRESP, NTGRESP & BESTRESP	Yes	Req	Char	--
RS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	VISIT	Visit name	Must contain "UNSCH" for unscheduled	Yes	Perm	Char	
SV	SVSTDTC	Start Date/Time of Visit	--	Yes	Exp	Char	ISO 8601
SV	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
TA	ANCHDTC	Anchor date of assessment schedule	Variable in ADSL - no name determined	NEW		Char	
TA	MAXPRD	Maximum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	MINPRD	Minimum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	STOFFSET	Start time from anchor date		NEW		Char	ISO 8601 Duration
TA	TGTPRD	Length of assessment schedule		NEW		Char	ISO 8601 Duration
TR	TRACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
TR	TRDTC	Date/Time of Tumor Measurement	--	Yes	Exp	Char	ISO 8601

TR	TREVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
TR	TRLINKID	Link ID	--	Yes	Exp	Char	--
TR	TRLNKGRP		--	NEW		Char	--
TR	TRSTAT	Tumor Assessment Status	NOT DONE	Yes	Perm	Char	ND
TR	TRSTRESC	Character Result/Finding in Std. Format	If TRTESTCD equals "TUMSTATE" Looks for PRESENT, ABSENT, UNEQUIVOCAL PROGRESSION	Yes	Exp	Char	--
TR	TRSTRESN	Numeric Result/Finding in Std. Format	--	Yes	Exp	Num	--
TR	TRTESTCD	Tumor Assessment Short Name	LDIAM, TUMSTATE, Looks for SUMLDIAM	Yes	Exp	Char	--
TR	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
TS	DCUTDTC	Data cut off date	--	New		Char	ISO 8601
TS	TSPARMCD	Trial Summary Parameter Short Name	PSSDDUR, PSCDUR	New	Req	Char	--
TS	TSVAL	Parameter Value	ISO Duration	New	Req	Char	--
TU	TUACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
TU	TUDTC	Date/Time of Tumor Identification	--	Yes	Exp	Char	ISO 8601
TU	TUEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
TU	TULINKID	Link ID	--	Yes	Exp	Char	--

TU	TULOC	Location of Tumor	--	Yes	Exp	Char	LOC
TU	TUMETHOD	Method of Identification	--	Yes	Exp	Char	
TU	TUSTRESC	Tumor Identification Result Std. Format	NEW	Yes	Exp	Char	
TU	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--

Please ensure that the following domains and variables are included in your CDISC data submissions. Although the CDISC Implementation guide lists many variables as permissible, in order for DOP2 to conduct efficient and timely reviews of the clinical trial data, most permissible variables should be considered as required variables. Please consult with the division on any permissible variables that you intend not to include in your data files so we can determine the impact this will have on the review process and the acceptability of the omission.

Table 2: Additional variables in SDTM and ADaM that are necessary for efficient review

DOMAIN	VARAIBLE	DATA TYPE
ADaM		
ADSL	STUDYID	C
ADSL	USUBJID	C
ADSL	TRT01A	C
ADSL	TRT01P	C
ADSL	ARM	C
ADSL	AGE	N
ADSL	AGEGR1	C
ADSL	SEX	C
ADSL	RACE	C
ADSL	TRTEDT	N
ADSL	TRTEDTM	N
ADSL	TRTSDT	N
ADSL	TRTSDTM	N
ADSL	DEATHDSC	C
SDTM		
AE	STUDYID	C
AE	USUBJID	C
AE	AEDECOD	C
AE	AEBODSYS	C
AE	AEREL	C
AE	AESEV	C
AE	AETOXGR	C

AE	AESTDTC	C
AE	AEENDTC	C
AE	AESTDY	N
AE	AEENDY	N
AE	AEDUR	C
CM	STUDYID	C
CM	USUBJID	C
CM	CMDECOD	C
CM	CMSTDTC	C
CM	CMENDTC	C
CM	CMENDY	N
CM	CMSTDY	N
CM	CMDUR	C
DM	STUDYID	C
DM	USUBJID	C
DM	AGE	N
DM	SEX	C
DM	RACE	C
DM	ARM	C
DM	RFENDTC	C
DM	RFSTDTC	C
DS	STUDYID	C
DS	USUBJID	C
DS	DSDECOD	C
DS	DSCAT	C
DS	DSSTDTC	C
DS	DSSTDY	N
EX	STUDYID	C
EX	USUBJID	C
EX	EXTRT	C
EX	EXDOSE	N
EX	EXSTDTC	C
EX	EXENDTC	C
EX	EXSTDY	N
EX	EXENDY	N
EX	EXDUR	C
LB	STUDYID	C
LB	USUBJID	C
LB	LBTEST	C
LB	LBSTRESN	N
LB	LBSTNRHI	N
LB	LBSTNRLO	N
LB	LBDTC	C
LB	LBDY	N
MH	STUDYID	C
MH	USUBJID	C
MH	MHDECOD	C
MH	MHBODSYS	C

VS	STUDYID	C
VS	USUBJID	C
VS	VSTEST	C
VS	VSSTRESN	N
VS	VSDTC	C
VS	VSDY	N

CDISC Oncology Domains

Introduction

Assessment of the change in tumor burden is an important feature of the clinical evaluation of cancer therapeutics: both tumor shrinkage (objective response) and disease progression are useful endpoints in cancer clinical trials[1]. RECIST (Response Evaluation Criteria in Solid Tumors)[2] has been widely adopted in solid tumor clinical trials where the primary endpoints are objective response or progression and is accepted by regulatory authorities as an appropriate guideline for these assessments. The SDTM domains presented here were developed with RECIST Criteria in mind. However, the domains are intended to represent data collected in clinical trials where tumors are identified and then repeatedly measured/assessed at subsequent timepoints and used in an evaluation of response(s). As such these domains would be equally applicable for criteria other than RECIST e.g. Chesson classification[3] in the assessment lymphomas, or, MacDonald Response[4] in the assessment of malignant gliomas.

The tumor assessment package consists of three SDTM domains based on the SDTM Findings Observation Class. The three domains are related but each domain has a distinct purpose:

TU (Tumor Identification): The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or independent assessor and in RECIST terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing information.

TR (Tumor Results): The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing information.

Clinically accepted evaluation criteria expect that a tumor identified by the tumor ID is the same tumor at each subsequent assessment. The TR domain does not include anatomical location information on each measurement record because this would be a duplication of information already represented in TU. This duplication of data was a deciding factor in multi-domain approach to representing this data.

RS (Response): The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

New variables:
--LINKID – The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). Therefore a new ID variable --LINKID is being proposed in order to support the linking requirements. The --LINKID variable is specifically designed to support a relrec dataset to dataset relationship. Values of LINKID could concatenate values of other variables when more than one variable are needed to do join data rows.

--ACPTFL – The Acceptance Flag identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

--EVALID – The Evaluator Specified variable is used in conjunction with TREVAL to provide an additional level of detail. When multiple assessors play the role identified in TREVAL, values of TREVALID will attribute a row of data to a particular assessor. For example TREVAL="INDEPENDENT ASSESSOR" and TREVALID="RADIOLOGIST 1". The --EVALID variable is not subject to Controlled Terminology. When --EVALID is populated --EVAL must also be populated.

References:

(1) E.A. Eisenhauera,*, P. Therasseb, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) *EUROPEAN JOURNAL OF CANCER 45 (2009) 228–247*
(2) RECIST Criteria - http://www.eortc.be/recist/
(3) Bruce D. Cheson, Beate Pfistner, et al. Revised Response Criteria for Malignant Lymphoma *Journal of Clinical Oncology. Vol 25 Number 5 Feb 10 2007*
(4) DR Macdonald, TL Cascino, et al. Response criteria for phase II studies of supratentorial malignant glioma *Journal of Clinical Oncology, Vol 8, 1277-1280*

1. Oncology Domains:

1.1. TUMOR IDENTIFICATION - TU

tu.xpt, Tumor Identification - Findings, Version 3. *x.x* …….. One record per identified tumor per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TU	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App.C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
TUSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TUGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUREFID	Reference ID	Char		Identifier	Internal or external identifier. Example:	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TULINKID	Link ID	Char		Identifier	Identifier used to link identified tumors to the assessment results over the course of the study.	Exp	
TUTESTCD	Tumor Identification Short Name	Char	*	Topic	Short name of the TEST in TUTEST. TUTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TUMIDENT, NEWTUMOR. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TUTEST	Tumor Identification Test Name	Char	*	Synonym Qualifier	Verbatim name of the test for the tumor/lesion identification. The value in TUTEST cannot be longer than 40 characters. Examples: Tumor Identification, New Tumor Identified. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TUCAT	Category for Tumor Identification	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TUSCAT	Sub-Category for Tumor Identification	Char		Grouping Qualifier	A further classification of the TUTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUORRES	Tumor Identification Result	Char	*	Result Qualifier	Result of the Tumor identification. Examples: When TUTESTCD=TUMIDENT (Tumor Identification), values of TUORRES might be: TARGET or NON-TARGET. When TUTESTCD=NEWTUMOR the value of TUORRES might be: Y When TUTESTCD=BENIGNAB the value of TUORRES might be: BENIGN RENAL LESIONS	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TUSTRESC	Tumor Identification Result Std. Format	Char	*	Record Qualifier	Contains the result value for all findings copied from TUORRES.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TUNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the Tumor Identification.	Perm	SDTM 2.2.3
TULOC	Location of the Tumor	CHAR	(LOC)	Record Qualifier	Used to specify the anatomical location of the identified tumor. Example: Gastrointestinal Tract. Note: When anatomical location is broken down and collected as distinct pieces of data that when combined provide the overall location information (e.g. organ / laterality /location / sub-location) then the additional information should added as supplemental qualifiers. See Assumption 3	Exp	SDTMIG 2.2.3
TUMETHOD	Method of Identification		*	Record Qualifier	Method used to identify the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3
TUEVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left *Null* when the Investigator provides the complete set of data in the domain. However the column should contain no *Null* values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with TUEVAL to provide an additional level of detail. When multiple assessors play the role identified in TUEVAL, values of TUEVALID will attribute a row of data to a particular assessor. TUEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2.. The TUEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5.	Perm	
TUACPTFL	Accepted Record Flag	Char	*	Record Qualifier	In cases where more than one independent assessor (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDTC	Date/Time of Tumor Identification	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDY	Study Day of Tumor Identification	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.1. ASSUMPTIONS FOR THE TUMOR IDENTIFICATION DOMAIN MODEL

TU Definition: The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or independent assessor and in RECIST terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing information.

1. The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). The --LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor.

2. The values of TUTESTCD and TUTEST will be relatively simple and will either represent that the Tumor is identified and categorized at screening or that the Tumor is identified as New (has appeared since the Screening assessment).

   Proposed TUTESTCD / TUTEST values for this domain:

TUTESTCD	TUTEST
TUMIDENT	Tumor Identification
NEWTUMOR	New Tumor Identified
BENIGNAB	Benign Abnormality
TUSPLIT	Tumor Split or Divided
TUMERGE	Tumor Merged or Coalesced

   During the course of a trial when a new Tumor (or lesion) is identified information about that new tumor may be collected to different levels of detail. The following three scenarios represent the most commonly seen data collection methods employed when a new Tumor (or lesion) is identified. The scenarios set out below are not intended to be exhaustive. The sponsor must decide the appropriate collection method based on their analysis needs or internal processes and it is possible that a sponsor's chosen method is not reflected in the scenarios presented below.

   a. The occurrence of a New Tumor is the sole piece of information that a sponsor collects because this is a sign of disease progression and no further details are required. In such cases a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y".

   b. The occurrence of a New Tumor and the anatomical location of that newly identified Tumor are the only collected pieces of information. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the TULOC variable would be populated with the anatomical location information (the additional location variables may be populated depending on the level of detail collected).

   c. A sponsor might record the occurrence of a New Tumor to the same level of detail as Target and Non-Target Tumors. In this case the occurrence of the new tumor and the anatomical location information, and also measure the New Tumor. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the identifier, TULINKID, would all be populated. The measurement/assessment of the New Tumor would be recorded in the TR domain.

3. TUCAT and TUSCAT have been included as they are standard domain variables however these columns would generally not be needed and so the variables are not included in the accompanying examples.

4. Anatomical Location information might be collected in a number of ways the simplest way is as a long text string and in these cases the text string is captured in the TULOC variable. However, anatomical location might also be collected through a number of distinct and separate variables (that might possibly be subject to controlled terminology) and in such cases the additional information would be recorded in the following Supplemental Qualifiers:

QNAM	QLABEL	Definition
TUSUBLOC	Sub-location of the Tumor	Anatomical location information with more specificity than a gross location
TULOCDET	Detailed Location Information	Detailed anatomical location information that would include details such as: direction (Superior, Posterior); relative direction (Proximal, Distal); axes (Dorsoventral, Mediolateral); planes (Sagittal, Coronal); and any other divisions or sub-anatomy information.
TUORGAN	Organ Affected	Actual Body Organ location of the tumor. This is more specific than Body Organ Class
TULAT	Tumor Location Laterality	Lateral location used to distinguish Right & Left sides. For example if a Tumor was located in the "Right Lung" then the TULOC and QNAM.TULAT values would be TULOC=LUNG; QNAM.TULAT=RIGHT.

5. The Acceptance Flag variable (TUACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

6. The Evaluator Specified variable (TUEVALID) is used in conjunction with TUEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TUEVAL variable. For example TUEVAL="INDEPENDENT ASSESSOR" and TUEVALID="RADIOLOGIST 1". The TUEVALID variable is not subject to Controlled Terminology. TUEVAL must also be populated when TUEVALID is populated.

7. The following proposed supplemental Qualifiers would be used to represent information regarding previous irradiation of a tumor when that information is known:

QNAM	QLABEL	Definition
PREVIR	Previously Irradiated	Indication of previous irradiation to a tumor.
PREVIRP	Irradiated then Subsequent Progression	Indication of documented progression subsequent to irradiation.

TUMOR RESULTS - TR

tr.xpt, Tumor Results - Findings, Version 3..*x x* …….. One record per tumor measurement/assessment per tumor per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TR	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App, 2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
TRSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TRGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
TRLINKID	Link ID	Char		Identifier	Identifier used to link the assessment result records to the tumor identification record.	Exp	
TRTESTCD	Tumor Assessment Short Name	Char	*	Topic	Short name of the TEST in TRTEST. TRTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: LDIAM, DIAM. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TRTEST	Tumor Assessment Test Name	Char	*	Synonym Qualifier	Verbatim name of the test or examination used to obtain the measurement or finding. The value in TRTEST cannot be longer than 40 characters. Examples: LONGEST DIAMETER, LONGEST PERPENDICULAR, AXIAL THICKNESS, VOLUME, AREA. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TRCAT	Category for Tumor Assessment	Char	*	Grouping Qualifier	Used to categorize assessments. Examples: Measurement Categorical	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TRSCAT	Sub-Category for Tumor Assessment	Char		Grouping Qualifier	A further classification of the TRTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TRORRES	Result or Finding in Original Units	Char		Result Qualifier	Result of the Tumor measurement/assessment as originally received or collected.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRORRESU	Original Units	Char	(UNIT)	Variable Qualifier	Original units in which the data were collected. The unit for TRORRES. Example: mm	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2
TRSTRESC	Character Result/Finding in Std Format	Char		Record Qualifier	Contains the result value for all findings, copied or derived from TRORRES in a standard format or standard units. TRSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in TRSTRESN	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESN	Numeric Result/Finding in Standard Units	Num		Result Qualifier	Used for continuous or numeric results or findings in standard format; copied in numeric format from TRSTRESC. TRSTRESN should store all numeric test results or findings.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESU	Standard Units	Char	(UNIT)	Variable Qualifier	Standardized unit used for TRSTRESN.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2 SDTMIG 4.1.5.1
TRSTAT	Tumor Assessment Status	Char	(ND)	Result Qualifier	Used to indicate a measurement was not done, or a tumor measurement was not taken. Should be Null if a result exists in TRORRES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRREASND	Reason Tumor Measurement Not Performed	Char		Record Qualifier	Describes why a measurement or test was not performed. Examples: BROKEN EQUIPMENT or SUBJECT REFUSED. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the Tumor measurement or assessment.	Perm	SDTM 2.2.3
TRMETHOD	Method used to identify the Tumor		*	Record Qualifier	Method used to measure the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TREVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left *Null* when the Investigator provides the complete set of data in the domain. However the column should contain no *Null* values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4
TREVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with TREVAL to provide an additional level of detail. When multiple assessors play the role identified in TREVAL, values of TREVALID will attribute a row of data to a particular assessor. TREVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The TREVALID variable would not be subject to CDISC Controlled Terminology. Note TREVAL must also be populated when TREVALID is populated. See Assumption 4	Perm	
TRACPTFL	Accepted Record Flag	Char	*	Record Qualifier	In cases where more than one independent assessor (e.g. where TREVALID has values of "RADIOLOGIST 1" & "RADIOLOGIST 2") provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TRDTC	Date/Time of Tumor Measurement	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TRDY	Study Day of Tumor Measurement	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.2. ASSUMPTIONS FOR THE TUMOR RESULTS DOMAIN MODEL

TR Definition: The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing information.

1. The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). The --LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor. TRLINKID is a required variable as the records in the TR domain must relate back to an identification record in TU.

2. TRTESTCD / TRTEST values for this domain (this is for illustration purposes these values will be published as Controlled Terminology):

TRTESTCD	TRTEST
AREA	Area
AXTHICK	Axial Thickness
DIAM	Diameter
LDIAM	Longest Diameter
LMAXSP	Major Axis Axial Plane, Long Diameter Target
LPERP	Longest Perpendicular
METVOLNO	Average Metabolic SUV
MJAX3SP	Major Axis 3D (All Planes)

MNAX3SP	Minor Axis 3D
MNAXSP	Minor Axis
MXSUVSSP	Maximum SUV (1 cm Spot)
MXSUVVSP	Maximum SUV (Single Voxel)
PCCHBL	Percent Change From Baseline
PCCHNAD	Percent Change From Nadir
PREVIR	Lesion Previously Irradiated
PREVIRP	Lesion Progressing Since Irradiated
PRODUCT	Product
RADDESP	Radio Density
SAXIS	Short Axis
SUMAREA	Sum of Area
SUMAXTHK	Sum of Axial Thickness
SUMLDIAM	Sum of Longest Diameter
SUMLPERP	Sum of Longest Perpendicular
SUMPDIAM	Sum of the product of the diameters
SUMPROD	Sum of Product
SUMVOL	Sum of Volume
VOLPETSP	Total Tumor Volume
VOLUME	Volume
XPRO3SP	Cross Product 3D
XPRODSP	Cross Product

Note: The sponsor should not derive results for any test indicated in the list above (e.g. “Percent Change From Nadir”) if the result was not collected. Tests would be included in the domain only if those data points have been collected on a CRF or have been supplied by an external assessor as part of an electronic data transfer. It is not intended that the sponsor would create derived records to supply those values.

3. The Acceptance Flag variable (TRACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

4. The Evaluator Specified variable (TREVALID) is used in conjunction with TREVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TREVAL variable. For example TREVAL=”INDEPENDENT ASSESSOR” and TREVALID=”RADIOLOGIST 1”. The TREVALID variable is not subject to Controlled Terminology. TREVAL must also be populated when TREVALID is populated.

RESPONSE – RS

rs.xpt, Response - Findings, Version 3..*x x* …….. One record per response assessment per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	RS	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App.C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
RSSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
RSGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
RSLINKID	Link ID	Char		Identifier	Used to link the response assessment to the appropriate measurement records (in TR) used to determine the response result.	Perm	
RSTESTCD	Response Assessment Short Name	Char	*	Topic	Short name of the TEST in RSTEST. RSTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TRGRESP, BESTRESP, SYMPTPD	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
RSTEST	Response Assessment Name	Char	*	Synonym Qualifier	Verbatim name of the response assessment. The value in RSTEST cannot be longer than 40 characters. Examples: Target Response, Best Overall Response, Symptomatic deterioration	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
RSCAT	Category for Response Assessment	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSSCAT	Sub-Category for Response Assessment	Char		Grouping Qualifier	A further classification of the RSTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
RSORRES	Response Assessment Original Result	Char		Result Qualifier	Result of the Response assessment as originally received, collected, or calculated.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTRESC	Response Assessment Result in Std Format	Char		Record Qualifier	Contains the result value for the response assessment, copied or derived from RSORRES in a standard format or standard units. RSSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in RSSTRESN	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTAT	Response Assessment Status	Char	(ND)	Result Qualifier	Used to indicate the response assessment was not performed. Should be Null if a result exists in RSORRES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSREASND	Reason Response Assessment Not Performed	Char		Record Qualifier	Describes why a response assessment was not performed. Examples: Subject does not have target lesions. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the response assessment.	Perm	SDTM 2.2.3
RSEVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left *Null* when the Investigator provides the complete set of data in the domain. However the column should contain no *Null* values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with RSEVAL to provide an additional level of detail. When multiple assessors play the role identified in RSEVAL, values of RSEVALID will attribute a row of data to a particular assessor. RSEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The RSEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5	Perm	
RSACPTFL	Accepted Record Flag	Char		Record Qualifier	In cases where more than one independent assessor (e.g. independent Oncologist) provides an evaluation of response this flag identifies the record that is considered to be the accepted evaluation.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSDTC	Date/Time of Response Assessment	Char	ISO 8601	Timing	Date may be derived if based on multiple dates of scans Exception: derived data in RS needed for reviewer	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSDY	Study Day of Response Assessment	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. May be from rand date not first dose date 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.3. ASSUMPTIONS FOR THE TUMOR RESPONSE DOMAIN MODEL

RS Definition: The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

1. The RSLINKID variable is used for values that support a relrec dataset to dataset relationship. RSLINKID would be required when a response evaluation relates back to an individual tumor.

2. RSTESTCD / RSTEST values for this domain(this is for illustration purposes these values will be published as Controlled Terminology):

RSTESTCD	RSTEST	Definition
TRGRESP	Target Response	
NTRGRESP	Non-target Response	
OVRLRESP	Overall Response	
BESTRESP	Best Response	
LESNRESP	Lesion Response	
SYMPTPD	Symptomatic Deterioration	

3. When an evaluation of Symptomatic Deterioration is recorded (which is symptomatic of progressive Disease) and additional description of the clinical symptoms is collected then that information would be recorded in the following Supplemental Qualifier:

QNAM	QLABEL	Definition
CLSYMP	Clinical Symptoms of PD	Textual description of clinical symptoms that led to the evaluation of Symptomatic deterioration

4. TS – TSPARM/TSVAL needed to represent the Response Criteria used in the clinical trial.

5. The Evaluator Specified variable (RSEVALID) is used in conjunction with RSEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the RSEVAL variable. For example RSEVAL=”INDEPENDENT ASSESSOR” and RSEVALID=”RADIOLOGIST 1”. The RSEVALID variable is not subject to Controlled Terminology. RSEVAL must also be populated when RSEVALID is populated.

MEETING ATTENDANCE LIST

Meeting between Hoffmann-La Roche (IND # 111723) and the Center for Drug Evaluation and Research.

DATE: April 7, 2015 TIME: 12:00-1:30 PM ET ROOM: WO22/Room 1421

NAME - Please print	AFFILIATION
Peter Marcos	Roche
Mireille METHUIN	ROCHE
BOGDANA BALAS	ROCHE
CHEZ MIN MURDOCH	ROCHE / GENENTECH
Ali Zeaiter	Roche
Annabelle MONNET	Roche
WALTER BORDOGNA	Roch
Anna BeryozKina	Roche
Michael Budde	Roche
PETRA BUSE	ROCHE
SARAH HOLLAND	ROCHE
Joyce WEAVER	FDA/DRISK
Olen Stephens	FDA/OND
Ruth Nitburg	FDA DOP2
Sachia Khasar	FDA/DHOT
Stacy Shord	FDA/OCP/DCPV
Rebecca Cohen	FDA/DOP2/OHOP
Whitney Helms	FDA/DHOT-DOP2
Laura Fernandez	FDA/OB/DBV
SHENGHUI TANG	Stat FDA
Erin Larkins	FDA/~~OHOP~~/CDER/OHOP/DOP2
PATRICIA KEEGAN	FDA/CDER/OND/OHOP/DOP2
G DAVIS	FDA/CDER/OND/OHOP/DOP2.

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/s/

GINA M DAVIS
04/16/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 111723

MEETING MINUTES

Hoffmann-La Roche Inc. c/o Genetech, Inc.
Attention: Kin Tang, Ph.D., R.Ph.
Group Director
1 DNA Way MS#242
South San Francisco, CA 94080

Dear Dr. Tang:

Please refer to your Investigational New Drug Application (IND 111723) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Alectinib (AF 802 ALK Inhibitor).

We also refer to the teleconference between representatives of your firm and the FDA on March 19, 2015. The purpose of the meeting was to discuss the manufacturing and control strategies for the Drug Substance and Drug Product and, the fileability of the (b) (4)% SLS formulation as the commercial formulation (b) (4)

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

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

Sincerely,

{See appended electronic signature page}

Olen Stephens, Ph.D.
Branch Chief, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes and Sponsor PowerPoint Presentation

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: CMC Meeting

Meeting Date and Time: Thursday, March 19, 2015 from 11:00 AM- 12:00 PM

Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, Maryland 20903

Application Number: 111723
Product Name: Alectinib
Indication: Treatment of ALK positive non-small cell lung carcinoma
Sponsor/Applicant Name: Hoffmann-La Roche Inc. c/o Genentech, Inc.

Meeting Chair: Olen Stephens, Ph.D.
Meeting Recorder: Rabiya Laiq, Pharm.D.

FDA ATTENDEES

Office of Pharmaceutical Quality
Office of New Drug Product
Olen Stephens, Ph.D., Acting Branch Chief, Division of New Drug Products I
Rajiv Agarwal, Ph.D., Chemist
Elsbeth G Chikhale, Ph.D., Acting Biopharmaceutics Lead
Donna Christner, Ph.D., Acting Branch Chief, Division of New Drug API
Debasis Ghosh, Ph.D., CMC Reviewer
Cathy Tran-Zwanetz, Regulatory Business Process Manager Branch Chief
Rabiya Laiq, Pharm.D, Regulatory Business Process Manager

Office of Process and Facilities
Jennifer Maguire, Ph.D., Acting Branch Chief
Zhaoyang Meng, Ph.D., Process Quality Reviewer

Office of New Drugs-DOP2
Gideon Blumenthal, M.D., Lead Medical Officer
Erin Larkins, M.D., Medical Officer

Office of Clinical Pharmacology
Stacy Shord, Pharm.D., OCP

SPONSOR ATTENDEES

Llorente Bonaga, Ph.D., Associate Program Director, Pharma Technical Regulatory Lead
Christiane Froehlich, Ph.D., Pharma Technical Development - Technical Development Leader
Dirk Spielvogel, Ph.D., Manufacturing Science & Technology – Drug Substance Process
Jenny Amrein, Ph.D., Manufacturing Science & Technology – Drug Substance Analytics
Carsten Timpe, Ph.D., Pharma Technical Development – Formulation Development
Joachim Lutz, Ph.D., Pharma Technical Development – Drug Product Analytics
Marc Lindenberg , Ph.D., Pharma Technical Development – Drug Product Analytics
Jens Lamerz, Ph.D., Biometrics – Non-Clinical Statistics
Kin Tang, Ph.D., R.Ph. Group Director, Pharma Technical Regulatory (calling from SSF)
Negar Sadrzadeh, Ph.D., Associate Program Director, Pharma Technical Regulatory (calling from SSF)
Jean-Philippe Crochard, Ms.c., Technical Regulatory Affairs Manager, Pharma Technical Regulatory
Mireille Methlin Costanzer, Pharm D., Pharma Development Regulatory, Global Regulatory Leader
Sarah Holland, Global Product Strategy, D.Phil. Oxon, MBA, Life Cycle Leader
Larry John Cain, Ph.D., Group Head, Pharma Technical Regulatory

1.0 BACKGROUND

The purpose of meeting is to discuss the manufacturing and control strategies for the Drug Substance and Drug Product and, the fileability of the (b)(4)% SLS formulation as the commercial formulation (b)(4) FDA sent Preliminary Comments to Hoffmann-La Roche Inc. c/o Genentech, Inc. on Thursday, March 12, 2015.

2. DISCUSSION

Question 1: A comprehensive assessment of potential genotoxic impurities originating from the commercial Drug Substance process and from the starting materials was performed and presented to the Agency in the EOP2 Briefing Package. Based on this assessment, two Class (b)(4) genotoxic impurities were identified: (b)(4). In addition, two groups of potential genotoxic impurities were identified: (b)(4) that may arise in the Drug Substance manufacturing process. An agreement was reached with the Agency concerning the control strategy for (b)(4) (Attachment A).

Does the Agency agree with the following elements pertaining to the control of genotoxic impurities?

- Use of ICH M7 less-than-lifetime (LTL) acceptable intakes for the control of Class (b)(4) and Class (b)(4) impurities.
- Acceptability of final control strategy for the (b)(4).
- Acceptability of the alternative control strategy for the (b)(4) that is based on the conclusions of the risk assessment conducted for the (b)(4) of (b)(4)

FDA Response: *From a CMC standpoint, ICHM7 LTL may be considered to calculate the permitted exposure level for Class* (b) (4) *and Class* (b) (4) *impurities.*

The proposed control strategy for the (b) (4) *compounds appears to be rational. The carryover model for risk assessment, impurity specification of the starting material* (b) (4)*, purging factors and analytical validation as a second control point demonstrate a multivariate comprehensive approach towards limiting the level of potential* (b) (4) *impurities. However, the adequacy of the information will be determined at the time of NDA review.*

The proposed alternative control strategy for the (b) (4) *based on an evaluation of the risk of formation of the* (b) (4) *at levels that could raise concerns appears to be reasonable. However, the adequacy of the information will be determined at the time of NDA review.*

Justification for control of these genotoxic impurities should be included in your NDA submission.

Discussion: The sponsor accepted FDA's response, no discussion occurred.

Question 2: The level of (b) (4) Drug Substance is controlled by (b) (4) . This ensures control of the (b) (4) Drug Substance. This controlled level of (b) (4) Drug Substance does not have an impact on the Drug Product critical quality attributes (CQAs) such as dissolution. Therefore, the (b) (4) Drug Substance specification. No further controls in the Drug Substance and Drug Product have been implemented. Does the Agency agree with the Sponsor's proposed control strategy for the Drug Substance (b) (4) ?

FDA Response: *No, based on the information provided in the meeting package, it is premature to remove testing for* (b) (4) *in the drug substance. During NDA review, when all developmental data is submitted for review, FDA will consider proposals to remove* (b) (4) .

Discussion: The sponsor provided an overview of their intended justification and data package to support removal of (b) (4) . The FDA responded that the rational for removing (b) (4) and proposed data package to support the proposal appears reasonable. As with other issues, the adequacy of the data and proposal to remove (b) (4) will be determined at the time of review of the NDA.

Question 3: The control strategy for alectinib hard capsules, 150 mg has been established based upon a Quality Risk Management process that will ensure process robustness and produce a product that meets the desired quality. Does the Agency agree with the Sponsor's proposed control strategy for the Drug Product?

FDA Response: *The described preliminary control strategy seems reasonable for the product under development. Evaluation of the control strategy will occur during NDA review in the context of supporting data to establish process parameters, in-process controls, and release specifications. Additionally, please include the following in your submission which are currently missing from your control strategy:*

a) *Discuss how the* (b) (4) *was optimized* (b) (4)

b) *Add an objective in-process control to* (b) (4) *end point.*

c) *We note that the manufacturing process* (b) (4)

d) *We note that you do not intend to monitor* (b) (4) *for the 150 mg strength capsule. This may be acceptable based on the drug* (b) (4) *for a sufficient number of commercial batches to demonstrate that* (b) (4) *is achieved and that routine testing is unnecessary.*

e) *You have proposed average* (b) (4) .

Discussion: The sponsor provided a summary of their manufacturing data that demonstrates a lack of correlation between any drug product CQA and after (b) (4) The FDA responded that no correlation is apparent in the presentation. In the NDA submission, data will be necessary to demonstrate that the variability observed (b) (4) resulting from the commercial process will not adversely impact product performance, specifically dissolution.

Question 4: Drug Substance and Drug Product Proposed Commercial Specification
Does the Agency agree with the proposed commercial specification for alectinib HCl Drug Substance and Drug Product?

FDA Response:

Drug Substance Specification:
The proposed specification for drug substance appears to be consistent with ICH and FDA guidelines. However, the adequacy of the information will be determined at the time of NDA review.

Please note that the exclusion of critical quality attributes like (b) (4) *from drug substance specification must be adequately justified in the NDA (refer also to the response to Question 2).*

Drug Product Specification:

In general the specification for the drug product is reasonable, however, we recommend that you include the test for (b) (4) *at release and during stability testing until sufficient experience is gained. The acceptance criterion of each test is a review issue and will be evaluated at the time of the NDA review.*

The microbial limits specifications used in the stability program appear adequate. For the drug product release testing listed in Table 25 of the meeting package, specify the USP method used (i.e. UPS <61> and USP <62>) and the proposed limits for each of the tests instead of "corresponds" that is currently provided.

Regarding the dissolution acceptance criteria for the proposed drug product, we recommend that you have multi-point dissolution acceptance criteria with an acceptance range of (b) (4) *% (mean* (b) (4) *%) for the middle time point, and NLT* (b) (4) *% at the last time point. The dissolution acceptance criteria should be determined based on dissolution data from the lots used in the clinical trials and primary stability studies.*

We remind you that in your NDA, you should provide the complete detailed dissolution method development report.

Discussion:
The sponsor provided data to support the proposed dissolution acceptance criteria of (b) (4) % at 30 minutes and Q = (b) (4) % at 75 minutes. The FDA responded that the data presented in this teleconference should be included in the NDA. FDA stated that the proposed dissolution acceptance criteria are wider than what we recommended in the (FDA) response to question 4. Furthermore, the FDA encouraged the sponsor to evaluate manufacturing process parameters that could be tightened to enable smaller ranges for the middle dissolution time point. FDA stated that full dissolution profiles should be collected during the stability studies, since the sampling time points are not yet finalized. It should be noted that L2 testing and sometimes L3 may be needed for some drug product batches. The dissolution acceptance criteria will be reviewed in light of full dissolution and manufacturing data at the time of NDA review.

Question 5: Does the Agency agree that the Sponsor's plan to provide 3 months accelerated and long-term site-specific stability data in the commercial packaging (250 mL round high-density polyethylene [HDPE] bottles with plastic child-resistant cap with integrated desiccant) adequately supports the use of a different container closure system and packaging site for the commercial product from that used for the primary registration batches?

FDA Response: *Yes it is acceptable.*

Discussion: The sponsor accepted FDA's response, no discussion occurred.

Additional FDA Comment: (Provided as part of preliminary meeting comments)
We request that you provide a report to FDA about the investigation of the root cause for the observed differences in the dissolution profiles between drug products containing SLS from different sources in the NDA submission.

Additional Discussion: As discussed in the teleconference, you anticipate submitting a prior approval supplement for a new formulation after approval of your NDA with the current formulation. FDA's understanding of the content of the supplement suggests that this supplement will be managed by the Office of Program and Regulatory Operations (OPRO) within the Office of Pharmaceutical Quality.

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/s/

RABIYA LAIQ
03/23/2015

OLEN M STEPHENS
03/23/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 111723

MEETING MINUTES

Hoffmann-La Roche Inc.
C/o Genentech, Inc.
Attention: Jerald Grace, Pharm.D., Program Manager, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080

Dear Dr. Grace:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AF-802 (RO5424802).

We also refer to the post-breakthrough designation meeting between representatives of your firm and the FDA on July 22, 2013. The purpose of the meeting was to discuss the clinical, nonclinical and clinical pharmacology development plans of the investigational product AF-802 (RO5424802) for the treatment of locally advanced or metastatic NSCLC with ALK gene rearrangement as detected by a Food and Drug Administration (FDA)-approved test and who have progressed on crizotinib therapy.

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

If you have any questions, call me at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Gina M. Davis, M.T.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Post-Breakthrough Designation
Meeting Date and Time:	July 22, 2013 from 2:00 PM - 3:00 PM
Meeting Location:	CDER WO 22**,** Room 1421
Application Number:	111723
Product Name:	AF-802 (RO5424802)
Indication:	For the treatment of Non-Small Cell Lung Cancer (NSCLC)
Sponsor/Applicant Name:	Hoffmann-La Roche, Inc.
Meeting Chair:	Gideon Blumenthal
Meeting Recorder:	Gina Davis

FDA ATTENDEES

Office of Hematology and Oncology Products
Patricia Keegan, M.D., Director, Division of Oncology Products 2 (DOP 2)
Gideon Blumenthal, M.D., Cross-Discipline and Medical Team Lead, DOP 2
Sean Khozin, M.D., Medical Officer, DOP 2
Gina M. Davis, M.T. Regulatory Health Project Manager (DOP 2)
Whitney Helms, Ph.D., Supervisor, Division of Hematology Oncology Toxicology (DHOT)
Sachia Khasar, Ph.D., Toxicology Reviewer, DHOT

Office of Clinical Pharmacology
Hong Zhao, Ph.D., Team Lead, Division of Clinical Pharmacology V (DCP V)
Stacy Shord, Pharm.D, Clinical Pharmacology and Genomics Reviewer, DCP V
Kevin Krudys, Ph.D., Reviewer, Division of Pharmacometrics

Office of Translational Sciences
Rosane Charlab Orbach, Ph.D., Genomics Acting Team Lead

Office of Biostatistics
Kun He, Ph.D., Statistical Team Lead, Division of Biometrics V (DB V)
Jonathon Norton, Ph.D., Statistical Reviewer, DB V

Office of New Drug Quality Assessment
Ali Al Hakim, Ph.D., Branch Chief, Office of New Drug Quality Assessment (ONDQA)
Liang Zhou, Ph.D., Team Lead, ONDQA
Angelica Dorantes, Ph.D., Biopharmaceutics Team Leader, ONDQA

SPONSOR ATTENDEES

Chris Bowden, M.D. Vice President, Product Development Clinical Oncology
Nathan Winslow Signaling Franchise Head, Product Development Regulatory
Mireille Methlin, PharmD Global Regulatory Leader, Product Development Regulatory
Jerald Grace, PharmD Program Manager, Product Development Regulatory

Ruey-Min Lee, MD, PhD Translational Medicine Leader, Pharma Research and Early Development
Laura Di Laurenzio, PhD Project Team Leader, Pharma Research and Early Development
Peter Morcos, PharmD Senior Scientist, Clinical Pharmacology
Steve Blotner, MS Senior Statistical Scientist
Kin Tang, PhD Pharma Technical Regulatory Leader
Li Yu, PhD Drug Metabolism and Pharmacokinetics Project Leader, Pharma Research and Early Development
Sven Kronenberg, PhD, Toxicology Project Leader, Pharma Research and Early Development DABT
Ilze Bara, MD Clinical Science Leader, Senior Medical Director Product Development Oncology

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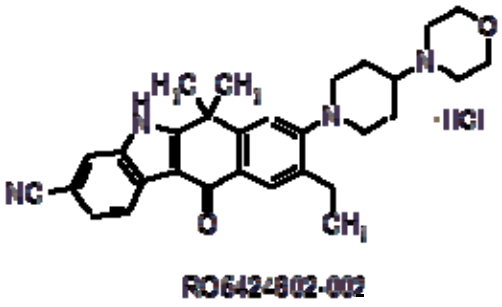
1.0 BACKGROUND

On April 18, 2013, Hoffmann-La Roche, Inc. (Roche) submitted a meeting request to discuss the clinical, nonclinical and clinical pharmacology development plans of the investigational product AF-802 (RO5424802) for the treatment of locally advanced or metastatic NSCLC with ALK gene rearrangement as detected by a Food and Drug Administration (FDA)-approved test and who have progressed on crizotinib therapy.

On May 1, 2013, Roche submitted a request for breakthrough therapy designation, which was granted on June 26, 2013. This meeting was requested to discuss and gain advice on Roche's clinical, non-clinical, and clinical pharmacology development plans for AF-802 (RO5424802).

AF-802 (RO5424802) is a small molecule that is an inhibitor of anaplastic lymphoma kinase (ALK). An immediate release 150-mg capsule formulation of AF-802 (RO5424802/F03) has been developed, containing RO5424802-002 (equivalent to 150 mg of the free base) and is packaged in high-density polyethylene bottles with plastic closure and desiccant and stored at (b) (4) (b) (4)C.

Chemical Name and Structure

Structural Formula	 RO5424802-002
Chemical Name	9-Ethyl-6, 6-dimethyl-8-[4-(morpholin-4-yl)piperidin-1-yl]-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile hydrochloride

Nonclinical studies completed or planned to support the development of RO5424802 as described in this package include numerous pharmacology and pharmacokinetic studies, genetic toxicology studies, GLP-compliant 4- and 13-week repeated dose toxicology studies in two species and GLP-compliant embryofetal development studies in two species (dose-range findings studies with positive results for embryotoxicity).

The clinical development program for RO5424802 is comprised of three ongoing Phase 1/2 studies and a planned study intended to support marketing approval (see table below).

Overview of the Ongoing Clinical Studies with RO5424802

Protocol No.	Phase	Objectives	Design	Population	N	Dosing Regimen/ Route	Status
AF-001JP	I/II	Safety, tolerability, efficacy, PK, investigation of food effect, effect on QT interval of RO5424802	PhaseI(Part1): Open-label dose escalation PhaseII(Part2): Expansion	Japanese, chemotherapy failed, crizotinib-naïve, ALK-positive NSCLC patients	Part1: n = 24 Part2: n = 46	20, 40, 80, 160, 240, 300 (fed/fasted) mg BID	Part1: completed; Part2: ongoing
NP28761/ AF-002JG	I/II	Safety, tolerability, efficacy, PK, effect on QT interval of RO5424802	PhaseI(Part1): Open-label dose escalation PhaseII(Part2): Expansion	United States, , chemotherapy failed, crizotinib-failed, ALK-positive NSCLC patients	Part1: n = ~30 Part2: n = 85	300 (fasted/fed), 460, 600, 760, 900 mg BID under fed conditions in Part 1 to determine RP2D to be used in Part 2 expansion	Part1: ongoing
NP28673	I/II	Safety, tolerability, efficacy, PK, effect on QT interval of RO5424802	PhaseI(Part1): Open-label, dose escalation PhaseII(Part2): Open-label, single arm, registration trial PhaseII (Part3): Post-progression treatment	Global, chemotherapy failed or naive, crizotinib-failed, ALK-positive NSCLC patients	Part1: n = up to 12 Part2: n = up to 130	600 and 900 mg BID under fed conditions (Part 1) to determine RP2D to be used in Part 2	Part1: ongoing

Studies NP28761/AF-002JG and NP28673 are single-arm, dose-finding and activity-estimating trials. The main objective of part 2 portions of Studies NP28761/AF-002JG and NP28673 is to evaluate the efficacy and safety of RO5424802 and demonstrate a positive benefit-risk ratio in patients with ALK rearrangement-positive NSCLC who have progressed on crizotinib. Both studies have overall response rate (ORR) as the primary endpoint with progression free survival (PFS), overall survival (OS), duration of response (DOR), and central nervous system (CNS) response and relapse rate as secondary endpoints. The results of these two studies, together with the results of Study AF-001JP performed in Japan, will be used as the basis for a request for accelerated approval under the provisions of 21 CFR 314 Subpart H.

- Part 2 of Study NP28761/AF-002JG will enroll 85 patients who will be treated orally BID with a dose chosen in Part 1. Assuming that the true ORR is 65%, then 85 patients are estimated to provide 80% power to reject a null hypothesis that the ORR is 50% (the lower limit of 95% CI will exclude 50%) The study will include a non-binding futility analysis of the first 30 patients.

- Part 2 of Study NP28673 will enroll a core group of 85 patients who received prior chemotherapy and progressed on crizotinib, as well as an additional "unpowered" cohort of 45 patients who are chemotherapy-naïve. The power calculations for Part 2 are the same as those for Study NP28761/AF-002JGl. Part 2 will also include a non-binding futility analysis of the first 30 patients, regardless of prior chemotherapy.

Roche also plans to conduct a confirmatory randomized (1:1), multicenter, active-controlled, open-label study (Study BO28984) to compare RO5424802 versus crizotinib in patients with advanced ALK rearrangement-positive NSCLC who are treatment-naive or who have received one line of standard platinum-based chemotherapy only. Roche states that the confirmatory trial will be ongoing at the time of filing for accelerated approval.

Patients in the experimental arm of Study BO28984 will receive RO5424802 at the RP2D dose used in Study NP28761/AF-002JG, and patients in the control arm will receive crizotinib at 250 mg BID, as per FDA-approved Prescribing Information. The primary endpoint of Study BO28984 will be PFS based on the assessment by an Independent Review Committee. A total of 298 patients will be enrolled. Roche states that 171 PFS events will be required to achieve 80% power to detect a hazard ratio of 0.65 for RO5424802 versus crizotinib at a two-sided alpha level of 5% (i.e., an increase from 9.2 months in the crizotinib arm to 14.2 months in the RO5424802 arm). The primary analysis will be a stratified log-rank test performed on the intent to treat (ITT) population. One interim analysis will be performed after 114 (67%) events for efficacy and futility. An O'Brien-Fleming spending function is used with an alpha allocation of 0.0121 at the interim analysis; the alpha for the final analysis is 0.0463. The futility stopping boundary is specified as non-binding.

Major secondary endpoints include central nervous system PFS, objective response rate, duration of response, and OS. The protocol synopsis does not specify the timing of the final OS analysis. No procedure is proposed to adjust for multiplicity in testing the secondary endpoints.

2.0 OBJECTIVES

- To obtain agreement on the following aspects of the RO5424802 development plan in support of the proposed indication
- The proposed clinical development plan
- The proposed non-clinical development plan
- The proposed clinical pharmacology development plan

3.0 SPONSOR SUBMITTED QUESTIONS

Clinical

1. Does the Agency agree that the two Phase I/II studies (Studies NP28761/AF-002JG and NP28673) with a primary endpoint of objective response rate (ORR) and a secondary endpoint of duration of response (DOR) according to RECIST, and the pooled safety database inclusive of the Phase II study in Japan, are sufficient to support an accelerated approval for the proposed indication?

   FDA response: FDA agrees that results from Studies NP28761/AF-002JG and NP28673, with 250 patients treated at the RP2D dose to be marketed in the United States in addition to the inclusion of the 70 patients from Study AF-001JP in the pooled safety database, can potentially permit a substantive review for accelerated approval. The clinical significance of the ORR and the adequacy of the data to support accelerated approval will consider the magnitude and duration the responses in a risk-benefit analysis at the time of review.

   Roche's July 21, 2013, response: The Sponsor acknowledges FDA's feedback. No further discussion required.

   Discussion during the meeting: FDA acknowledged Roche's July 21, 2013, comments above and no discussion occurred.

2. The two Phase I/II studies (Studies NP28761/AF-002JG and NP28673) are designed to characterize the efficacy and safety of RO5424802 for the treatment of patients with locally advanced or metastatic NSCLC that is ALK-positive. Does the Agency agree that the proposed treatment population is adequately defined per the eligibility criteria?

   FDA response: FDA does not agree with the inclusion of stage IIIB NSCLC patients (according to the American Joint Committee on Cancer Staging Atlas, 7th edition) who may be eligible for multimodality treatment as candidates for RO5424802 therapy. FDA agrees with the Roche's definition for "crizotinib failure" as patients with prior treatment with crizotinib and progression based on RECIST criteria, version 1.1, with the last dose of crizotinib within 60 days of the first dose of study treatment.

   In addition, Roche should clarify how patients are being assessed for ALK rearrangement status in studies NP28761/AF-002JG and NP28673, as there are some discrepancies in this definition in Roche's meeting package.

   Roche's July 21, 2013, response: The Sponsor acknowledges FDA's feedback. To clarify, patients enrolled in studies NP28761/AF-002JG and NP28673 are required to have prior ALK rearrangement status established by the FDA approved Vysis ALK Break-Apart FISH Probe Kit. No further discussion is required.

Discussion during the meeting: FDA acknowledged Roche's July 21, 2013, clarification above and no discussion occurred.

3. Does the Agency agree with the statistical assumptions and statistical power for the two Phase I/II studies (Studies NP28761/AF-002JG and NP28673) with a primary endpoint of ORR according to RECIST to support registration of RO5424802?

FDA response: In a single arm trial, the sample size should be chosen such that the lower limit of the 95% confidence interval for the point estimate represents a clinically relevant response. FDA recommends that Roche uses exact statistical methods for testing the binomial proportion and constructing a confidence interval.

Roche's July 21, 2013, response: The Sponsor has assessed current assumptions and proposes to change the target ORR from 65% to 50%, in which case a null hypothesis of 35% would be rejected (the lower limit of the 95% CI would exclude 35%). The Sponsor believes this would still represent a clinically relevant response. Does the FDA agree?

Additionally, the Sponsor would like to confirm, considering the sample size for the two Phase I/II studies will be greater than 85 patients, does the FDA recommend that Roche use the "Exact Method" for calculating confidence intervals?

Discussion during the meeting: FDA stated that Roche's proposal to modify the protocol to target an overall response rate of 50% with the lower bound of 35% is acceptable. However, whether the estimated ORR and accompanying confidence interval are sufficient to support a request for accelerated approval would be a review issue. FDA stated that the results of the trial would be evaluated considering the safety profile of the drug and the durability of response. FDA further stated that the results would need to demonstrate a substantial advance over available therapy to be considered for accelerated approval under subpart H.

FDA stated that Roche should use a method for the confidence interval that can be shown to provide 95% coverage with the sample size used.

4. Does the Agency agree that positive results from the proposed Phase III study could be used to support conversion of RO5424802 from accelerated approval to full approval?

FDA response: Yes, FDA agrees that the proposed confirmatory trial could be used to support conversion of RO5424802 from accelerated approval to regular approval provided the risk-benefit is favorable. FDA advises against early termination of trial for efficacy (evidence of improved PFS for RO5424802 over crizotinib treatment). The results of the interim analysis can lead to an overestimation of the treatment effect of RO5424802. See additional comment #16.

Roche's July 21, 2013, response: The Sponsor acknowledges FDA's feedback. No further discussion required.

Discussion during the meeting: FDA acknowledged Roche's July 21, 2013, comments above and no discussion occurred.

Clinical Pharmacology

5. Does the Agency agree that the overall clinical pharmacology program, including the planned clinical pharmacology studies and their proposed study designs, is sufficient to support the initial registration of RO5424802?

FDA response: No. FDA recommends that Roche conduct the following the studies in addition to the planned studies listed in Table 13 of the meeting background package during the development of RO5424802.

a. A food effect study with the to-be-marketed drug product following the FDA Guidance for Industry entitled "*Food-Effect Bioavailability and Fed Bioequivalence Studies*" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070241.pdf.

b. A study to assess the effect of drugs known to alter the gastrointestinal pH (e.g., proton pump inhibitors, H_2 antagonists and antacids) on the pharmacokinetics of RO5424802 as it demonstrates pH dependent solubility. The study may be conducted in a gated manner, first evaluating the effect of a proton pump inhibitor (PPI) on the exposure of RO5424802. In the event that concomitant administration of a PPI has a large impact on RO5424802 exposure, H_2 antagonists and antacids should be subsequently evaluated.

c. A study to determine the appropriate dose in patients with mild, moderate or severe hepatic impairment in accordance with FDA draft Guidances for Industry entitled "*Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf.

The results of the planned mass balance and absolute bioavailability studies will determine whether a study is needed to identify the appropriate doses in patients with mild, moderate or severe renal impairment.

Furthermore, FDA recommends that Roche calculate the appropriate R values for the completed and planned *in vitro* studies as listed in the FDA draft Guidance for Industry *"Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations"* to determine the need for additional pharmacokinetic drug interaction studies. The calculated R values along with the protocols for any additional proposed clinical pharmacology studies in humans to address the potential pharmacokinetic interactions should be submitted for FDA review.

Roche should determine the ability of the M4 metabolite to act as a substrate, inducer or inhibitor of cytochrome P450 enzymes, transporters and conjugating enzymes.

Roche should consider conducting studies with a P-glycoprotein substrate and with a BCRP substrate as the *in vitro* data suggest that RO5424892 has the potential to inhibit these transporters in humans.

Roche's July 21, 2013, response: The Sponsor thanks the FDA for their feedback and would like to clarify four points:

- The Sponsor would like to confirm that the Agency agrees with the Sponsor's currently proposed Clinical Pharmacology studies (Table 13) and study designs including the use of Healthy Volunteers in planned single dose crossover studies?

  Discussion during the meeting: FDA agreed with the proposed studies and study designs listed in Table 13. Roche agreed to provide the protocols for these proposed studies for FDA review before starting these studies.

- Roche will start a Food Effect and PPI DDI study with the current formulation in the current time. For the PPI DDI, the Sponsor would like to confirm that a single RO5424802 dose crossover study could be acceptable to evaluate the potential effect of an antisecretory agent on RO5424802, as single dose pharmacokinetics may be sensitive to discern effects from a potential interaction mediated through absorptive process?

  - A single dose crossover study design for anti secretory DDI's has been utilized for other tyrosine kinase inhibitors with pH dependent solubility (e.g. crizotinib, nilotinib, imatinib, erlotinib, dasatinib, etc).

  Does the Agency agree with this approach?

  Discussion during the meeting: FDA agreed with the Roche's proposal to conduct a PPI DDI study utilizing a single dose cross-over design with multiple doses of PPI. Roche agreed to provide the protocol for the food effect and PPI DDI studies for FDA review before starting these studies.

- For the hepatic impairment study, the Sponsor plans to use data generated from the proposed mass balance study as well as analyses of the Phase 2 data (e.g. use the planned population PK analysis to identify/evaluate any significant covariates related to hepatic function (e.g. liver function tests)) to guide and optimize (e.g. dose selection) a hepatic impairment study. Further, enrollment of cancer patients with varying degrees of hepatic impairment will likely pose significant recruitment challenges to the conduct/completion of the study within the submission timelines. Does the agency agree that this study along with any additional metabolic or transporter mediated DDIs (guided by R value

calculations) can be conducted in the post-marketing setting in light of the accelerated development plan and breakthrough designation for RO5424802?

Discussion during the meeting: FDA agreed that the hepatic impairment study along with any additional metabolic transporter mediated DDIs can be conducted in the post-marketing setting in light of the accelerated development plan and breakthrough designation for RO542802. Roche agreed to provide plans for these studies in the NDA submission.

- Regarding the M4 metabolite, Roche has provided a DMPK plan for characterization of M4 for the initial filing following ICH S9. (See Question 8 under nonclinical). In this plan, M4 will be only assessed as an inhibitor of major CYPs and transporters. It is the understanding of the Sponsor that FDA has accepted this plan in their response "…the characterization of the M4 metabolite appears sufficient to support the submission of a NDA." Roche would like to confirm that no additional studies (such as for a substrate, inducer, or inhibitor of conjugating enzymes) are required beyond our plan listed in Question 8.

  Discussion during the meeting: Roche agreed to provide a plan to determine the ability of the M4 metabolite to act as a substrate inhibitor or inducer of cytochrome P450 enzymes transporters and to initiate these studies as soon as is feasible. Roche agreed to propose additional clinical trials if warranted.

6. Does the Agency agree that the Sponsor's approach to rigorous QT/QTc evaluation in the ongoing clinical trials in lieu of conducting a separate dedicated QT/QTc study will be sufficient to assess the potential effect of RO5424802 on QT/QTc interval?

   FDA response: Roche's approach to characterize the potential effect of RO5424802 appears to be adequate. The final determination of the acceptance of the data to assess the risk of RO5424802 on QTc prolongation will be made at the time of NDA review.

   a. The dose is acceptable.

   b. The timing of ECG/PK collection times appears adequate.

   c. The sample size is acceptable.

   d. In most cases, a linear mixed effects modeling approach may be used to quantify the relationship between plasma concentrations (of the parent drug and/or metabolite(s)) and ΔQTc (baseline-adjusted). Based upon this relationship, the predicted population average ΔQTc and its corresponding upper 95% one-sided confidence interval bound may be computed at appropriate concentrations, e.g., the mean maximum plasma concentrations under therapeutic and supratherapeutic doses or other concentrations of interest).

   e. FDA encourages the exploration of the adequacy of the model fit to the assumption of linearity and the impact on quantifying the concentration response

relationship. Therefore, diagnostic evaluation is expected as part of the application of the method recommended here. Additional exploratory analyses (via graphical displays and/or model fitting) include accounting for a delayed effect and the justification for the choice of pharmacodynamic model (linear versus nonlinear).

f. FDA recommends that Roche incorporate the following elements into the assessment of the ECGs recorded during the studies:

- Blinding of ECG readers to treatment, time, and day (i.e., Day -1; Day 1) identifiers
- Review of ECGs from a particular subject should be performed by a single reader
- Pre-specify the lead for interval measurements
- Baseline and on-treatment ECGs should be based on the same lead

FDA is also interested in the effects of the RO5424802 on other ECG intervals and changes in waveform morphology. Please submit PR and QRS interval data with the study report and descriptive waveform morphology changes.

g. When Roche submits the QT study report, include the following items:

- Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
- Electronic copy of the study report
- Electronic or hard copy of the clinical protocol
- Electronic or hard copy of the Investigator's Brochure
- Annotated CRF
- A data definition file which describes the contents of the electronic data sets
- Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure response analyses
- Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in the report, e.g. QTcB, QTcF, QTcI, if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable).
- Data set whose QT/QTc values are the average of the above replicates at each nominal time point
- Narrative summaries and case report forms for any
  - Deaths
  - Serious adverse events
  - Episodes of ventricular tachycardia or fibrillation
  - Episodes of syncope

- Episodes of seizure
- Adverse events resulting in the subject discontinuing from the study

- ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
- A completed Highlights of Clinical Pharmacology Table

h. Advancing in this field – and possibly reducing the burden of conducting QT studies – depends critically upon obtaining the most comprehensive understanding of existing data. Please consider making the data, at least placebo and positive control data, available for further research purposes; see, for examples, the Data Request Letter at www.cardiac-safety.org/library.

Roche's July 21, 2013, response 6: The Sponsor thanks the FDA for their feedback and would like to clarify that:

Although the clinical studies intend to rigorously evaluate the potential effect of RO5424802 on ECG parameters including QT/QTc through collection of ECGs, the planned evaluation does not represent an E14 TQT study. As such, the Sponsor believes that some of the FDA recommendations in footnotes f, g, and h may not be applicable or appropriate in the planned setting:

- For footnote 'f' the Sponsor believes it will be not applicable or challenging to ensure blinding of ECG readers to treatment and time as this is a single treatment open-label study.
- Further, as patients will be on treatment for potentially several months to years it will unlikely be possible to ensure that reviews of the ECGs are performed by a single reader particularly at later timepoints in the study.
- As the ongoing clinical studies are not E14 TQT studies, the Sponsor does not believe it would be required to submit ECG waveforms to the ECG warehouse and since there is no placebo or positive control data footnote 'h' may not be appropriate/applicable.

Thus, could the FDA confirm that the Sponsor's intention to rigorously evaluate the potential effect of RO5424802 on ECG parameters including QT/QTc interval without meeting all the general requirements for E14 TQT studies (provided in footnotes f, g, and h) will be considered sufficient?

Discussion during the meeting: Roche stated that some elements of the QT evaluation as listed above are not appropriate given the design of the phase 2 study. FDA stated that modification of the plan as stated in bullets 1 and 2 is acceptable: however, submission of the ECG waveforms to the warehouse is required. Roche agreed to submit the ECG waveforms.

Nonclinical

7. Does the Agency agree that the nonclinical toxicology program is adequate to support the registration of the RO5424802 Drug Product?

FDA response: The studies described in the meeting package appear sufficient to support the submission of an NDA; however, the adequacy of the data will be determined during the review of application. The tabulated summaries in the meeting package do not appear to include pharmacology studies of the M4 metabolite described in the body of the package. Please include completed pharmacology/pharmacokinetic studies conducted using the M4 metabolite in the future NDA submission.

Roche's July 21, 2013, response: The Sponsor would like to clarify the request for M4 pharmacology/pharmacokinetic studies. The Sponsor would like to confirm that the M4 pharmacology studies are listed in Appendix 1 of the pre-meeting package (Report No. 1056380 and 1056381). Please note that there were no pharmacokinetic studies performed where M4 was dosed, rather, the M4 metabolite was measured in plasma following single dose of RO5424802 in rat and monkey (Section 11.3.2; page 74; Report No 1056255 and 1056256 in Appendix 1). In our study plan, we will confirm M4 exposure in monkeys after repeat daily dosing of RO5424802 for 1 week at 12 mg/kg. There are no *in vivo* pharmacology and PK studies planned with dosing of M4 in our package. With this clarification, are there any further pharmacology/pharmacokinetic studies requested to be included in the future NDA submission?

Discussion during the meeting: FDA stated that no additional in *vivo* pharmacology data is requested. Roche stated that no additional animal pharmacology and pharmacokinetic studies are planned. Those studies included in the table are complete and will be submitted at the time of the NDA submission.

8. Does the Agency agree that the Toxicology/Drug Metabolism and Pharmacokinetics (DMPK) package for characterization of the major metabolite M4 is sufficient to support the registration of RO5424802?

FDA response: Based on the information described in the meeting package, the characterization of the M4 metabolite appears sufficient to support the submission of a NDA.

Roche's July 21, 2013, response: The Sponsor acknowledges FDA's feedback. No further discussion required.

Discussion during the meeting: FDA acknowledged Roche's July 21, 2013, comments above and no discussion occurred.

Chemistry, Manufacturing and Controls and Biopharmaceutics

9. The Sponsor proposes to use the 150-mg hard capsule formulation currently being used in clinical studies as the market formulation. Does the Agency agree that the amount of

the inactive ingredient, sodium lauryl sulfate, of (b) (4) per 150-mg hard capsule in the planned registration dose is acceptable?

FDA response: No, FDA does not agree. The toxicological assessment provided for (b) (4) sodium lauryl sulfate (SLS) in the formulation of the drug product to be marketed (b) (4)

(b) (4) Hoffmann will need to provide further scientific justification to support the risk/benefit profile of this excipient (b) (4) in the proposed NDA if the formulation is not altered.

FDA strongly recommends (b) (4)

Roche's July 21, 2013, response 8: The Sponsor acknowledges the FDA's concern with the current formulation of RO5424802. While we are considering the Agency's recommendations, given the robust efficacy and safety data available to date, the recently received Breakthrough designation, and the unmet medical need in this patient population, we would like to clarify the Agency's suggestion with regards to providing "scientific justification that would be needed to support the risk/benefit profile of the excipient (b) (4) in the proposed NDA if the formulation is not altered."

To support the discussion on the risk/benefit profile for the use of this formulation at launch, the following nonclinical and clinical information is provided.

In support of the favorable clinical risk/benefit, the safety margins derived from SLS repeat dose toxicity testing in the rat are summarized below (Appendix 4, page 10). Based on mg/kg, a (b) (4) safety margin is derived for a total clinical SLS dose of (b) (4) mg ((b) (4)/day SLS, i.e. (b) (4)/day SLS) vs. the rat NOAEL of (b) (4)/day. Of note, GI tract toxicity as the safety determinant of SLS is not due to systemic toxicity, but a consequence of local irritation to the GI tract which is reflected by this approach to calculate safety margins. In addition, the SLS doses in the clinical trials with RO5424802

are divided into two separate doses per day rather than a single high dose which should reduce risks for acute toxicity of SLS.

Dose cohorts and estimated safety margins based on the NOAEL for SLS toxicity in the rat of (b) (4) /day

Cohort	RO5424802 Dose	Total SLS Dose ((b) (4) % of drug substance)	HED Safety Margin based on mg/m^2* (NOAEL)	Safety Margin based on mg/kg** (NOAEL)	Margin*** (LOAEL)
Cohort 1 (fasting)	300 mg BID				(b) (4)
Cohort 2 (non-fasting)	460 mg BID				
Cohort 3 (non-fasting)	600 mg BID				
Cohort 4 (non-fasting)	760 mg BID				
Cohort 5 (non-fasting)	900 mg BID				

*) HED: human equivalent dose using body surface scaling across species (rat scaling factor:6);

/*) Safety margin is based on human (b) (4) bodyweight and if no interspecies adjustment is done because at least local GI toxicity (major concern) is not due to systemic exposure.

***) Decreases in bodyweight gain at this dose without clear signs of GI irritation. Stomach lesion in rats by local irritant usually occurs in non-glandular region of the stomach, which is histologically similar to the skin, but equivalent structure is not present in human stomach.

As described in the pre-meeting package, patients received RO5424802 doses in ranges from 300-900 mg BID for greater than one year in some dose cohorts. Regarding risks, the most common risks for SLS are GI irritation presented with abdominal discomfort and diarrhea. In the current safety database of 70 patients in Japan and 40 patients in the US, there have been no reports of severe gastrointestinal adverse events (Grade 3 or higher). Based on the current clinical and nonclinical data, the toxicity contributed from SLS is minimal. Our current data suggests that the gastrointestinal safety profile of RO5424802 is at least comparable to crizotinib and other ALK inhibitors in development. (Shaw A, et al. ASCO 2013, XALKORI USPI).

In our ongoing Phase I/II studies, Roche is monitoring patients for GI related toxicity which are commonly reported SLS-related adverse events. In addition to routine monitoring, the Sponsor has a Data Safety Monitoring Board (DSMB) in place.

Based on nonclinical and clinical safety assessments, along with the favorable response data available to date (Section 9.2.4, page 43), the Sponsor believes RO5424802 will demonstrate a positive benefit/risk with the current formulation to support an initial launch. Pending favorable Phase II data from the two ongoing studies (i.e. safety database of 250 patients with RR of 50% and duration of response of at least 6 months) could the

Agency please clarify what additional data could be provided to support the risk/benefit profile of the drug product, in reference to the current formulation?

Discussion during the meeting: FDA stated (b) (4) that the IND does not provide adequate justification for safety based on nonclinical data. Roche should:

- Identify other formulations that have been investigated and the data showing that the these alternate formulations could not result in a commercially viable drug product.
- Provide adequate human clinical data, updated quarterly, justifying the safety of the proposed amount of SLS in the product.
- Consider an additional study (28-day study comparing old toxicology formulation to current clinical formulation).
- Provide data demonstrating (b) (4) % SLS. Provide data correlating rapid dissolution rate with bioavailability.

Whether these data would support approval of the current formulation would be contingent on the finding of an acceptable risk/benefit ratio in the proposed phase 2 studies supporting request for accelerated approval.

Roche intends to submit a request for a CMC meeting within the near future and plans to conduct a clinical-PK (relative bioavailability) trial using alternate formulations (b) (4)

FDA agreed to continue discussions on the acceptability on the proposed formulation for commercial marketing based on the data requested above.

ADDITIONAL COMMENTS

Clinical
Regarding Study NP28673:

10. For treatment with RO5424802 beyond progression in chemotherapy-naïve patients, the informed consent must contain an adequate discussion of the risks and benefits of platinum-based chemotherapy and note that the absence of data that such a practice is safe or effective. In addition, please note that this practice will not support a claim of treatment beyond progression, as the design of the proposed studies are not adequate to obtain substantial evidence of effectiveness for RO5424802 administered in this manner.

    Roche's July 21, 2013, response to additional comment #10: The Sponsor acknowledges FDA's feedback. No further discussion required.

Discussion during the meeting: FDA acknowledged Roche's July 21, 2013, response to additional comment # 10 and no discussion occurred.

11. In part 3 of the trial:
    a. Define dose limiting toxicities (DLTs)

    b. Enroll patients in sequential cohorts of six patients

    c. If there are 2 or more DLTs in the first six patients during the first cycle of treatment, institute dose reduction for patients receiving RO5424802 in combination with erlotinib.

    Roche's July 21, 2013, response to additional comment #11: The Sponsor acknowledges FDA's feedback. No further discussion required.

    Discussion during the meeting: FDA acknowledged Roche's July 21, 2013, response to additional comment # 11 and no discussion occurred.

12. FDA encourages Roche to request a meeting to discuss the clinical development plan for RO5424802 in patients with CNS metastasis. A detailed plan that can facilitate the assessment of the safety and efficacy of RO5424802 in ALK rearrangement-positive NSCLC patients with CNS metastasis would be required (b) (4)

    Roche's July 21, 2013, response to additional comment #12: The Sponsor acknowledges FDA's feedback. No further discussion required.

    Discussion during the meeting: FDA acknowledged Roche's July 21, 2013, response to additional comment # 12 and no discussion occurred.

13. In the clinical development plan for RO5424802, please consider inclusion of an exploratory analysis of ORR, DOR, and PFS as measured by volumetric CT versus standard RECIST v1.1 assessments.

    Roche's July 21, 2013, response to additional comment #13: The Sponsor acknowledges FDA's feedback. No further discussion required.

    Discussion during the meeting: FDA acknowledged Roche's July 21, 2013, response to additional comment # 13 and no discussion occurred.

14. Prior to initiation of the proposed Phase 3 trial (Study BO28984), FDA recommends that Roche (or their companion diagnostic partner) discuss their plans for using any non-FDA-approved companion diagnostic assay(s) for patient selection with CDRH.

Roche's July 21, 2013, response to additional comment #14: The Sponsor acknowledges FDA's feedback. No further discussion required.

Discussion during the meeting: FDA acknowledged Roche's July 21, 2013, response to additional comment # 14 and no discussion occurred.

Statistical Comments
Regarding Study BO28984:

15. The proposed primary endpoint of PFS assessed by an independent review committee is acceptable to FDA. Alternatively, Roche may consider submission of a proposal to conduct an audit of a randomly selected subset of patients to confirm investigator-assessed PFS. If Roche plans to use this latter option, then a detailed auditing plan that includes a strategy to detect potential assessment bias should be proposed. This auditing plan should include the percentage of patients to be audited, the method used to identify the subset of images to be audited, the method for comparing the PFS results obtained by local review with the PFS results of the audit, and the criteria for determining whether all images need to be audited. All images should be archived and easily accessible. If bias cannot be excluded based upon the audit, then FDA will consider an independent evaluation of all radiographic images to be necessary for assessment of the primary PFS endpoint.

    Roche's July 21, 2013, response to additional comment #15: The Sponsor acknowledges FDA's feedback. No further discussion required.

    Discussion during the meeting: FDA acknowledged Roche's July 21, 2013, response to additional comment # 15 and no discussion occurred.

16. FDA discourages interim analyses of PFS since the treatment effect of PFS tends to be liable to overestimation, is not robust, and is often not reproducible with immature data. However, if Roche chooses to continue having an interim analysis plan for PFS, please discuss with FDA before stopping the trial for efficacy.

    Roche's July 21, 2013, response to additional comment #16: The Sponsor acknowledges FDA's feedback. No further discussion required.

    Discussion during the meeting: FDA acknowledged Roche's July 21, 2013, response to additional comment # 16 and no discussion occurred.

17. Please provide a statistical analysis plan for OS including the difference to be detected, the power, the number of deaths for the final OS analysis, and the number of deaths for an interim OS analysis at the final PFS analysis.

    Roche's July 21, 2013, response to additional comment #17: The Sponsor acknowledges FDA's feedback. No further discussion required.

Discussion during the meeting: FDA acknowledged Roche's July 21, 2013, response to additional comment # 17 and no discussion occurred.

18. Results of secondary endpoints will generally not be considered unless there is persuasive evidence from the analysis of the primary endpoint. The secondary endpoints of which Roche intends to make claims need to be agreed by the Agency. In addition, the statistical analysis plan controlling for overall false positive rate at a level of 0.05 for those secondary endpoints must be specified.

Roche's July 21, 2013, response to additional comment #18: The Sponsor acknowledges FDA's feedback. No further discussion required.

Discussion during the meeting: FDA acknowledged Roche's July 21, 2013, response to additional comment # 18 and no discussion occurred.

Biopharmaceutics

19. Please also note the following FDA's general advice comments regarding the dissolution method development and setting of the dissolution acceptance criteria.

Ensure that the NDA contain a dissolution method development report that includes the following information:

a. Solubility data for the drug substance covering the pH range;

b. Detailed description of the dissolution test being proposed for the evaluation of the proposed drug product and the developmental parameters used to select the proposed dissolution method as the optimal test for the proposed product (*i.e., selection of the equipment/ apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.*). If a surfactant was used, the data supporting the selection of the type and amount of surfactant should be included. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete (*i.e., 15, 20, 30, 45, & 60 minutes*) and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. FDA recommends that at least twelve samples be used per testing variable;

c. Provide the complete dissolution profile data (*individual, mean, SD, profiles*) for the proposed drug product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*); and

d. Include the complete dissolution data for the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.). In general, the

testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e. aberrant formulations and manufacturing conditions) for the most relevant critical manufacturing variables (e.g. (b) (4) etc.).

The dissolution method report may also be provided under the IND for review and comments.

For setting of the dissolution acceptance criterion of the proposed drug product, the following points should be considered:

e. The dissolution profile data (*i.e., 15, 20, 30, 45, & 60 minutes*) from the clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criterion of the proposed drug product [i.e., specification-sampling time point and specification value].

f. The *in vitro* dissolution profile should encompass the timeframe over which at least (b) (4)% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.

g. The selection of the specification time point should be where Q = (b) (4)% dissolution occurs. However, if you have a slowly dissolving product or a poor-soluble drug, a two-point specifications option may be adequate for your product. The first time point should be during the initial dissolution phase (i.e., 15-20 minutes) and the second time point should be where Q = (b) (4)% dissolution occurs.

h. The dissolution acceptance criterion should be based on average in vitro dissolution data (n=12).

Roche's July 21, 2013, response to additional comment #19: The Sponsor acknowledges FDA's feedback. No further discussion required.

Discussion during the meeting: FDA acknowledged Roche's July 21, 2013, response to additional comment # 19 and no discussion occurred.

ACTION ITEMS

Hoffmann-La Roche agreed to submit a meeting request with the CMC team in the near future.

FDA stated that requests for informal teleconferences to address a limited number of questions can be supported with appropriate background of a few pages for the following topics;

- Studies in patients with ALK-positive NSCLC
- Studies in patients with CNS metastasis
- Plans for expanded access

ADDENDUM TO FINAL MEETING MINUTES

Please note that there are slight changes to our preliminary responses to question 5(a) and 5(b) sent via electronic (email) communication on July 18, 2013. The final meeting minutes contain the revised version. This addendum includes the preliminary responses to question 5(a) and 5(b) sent on July 18, 2013 as well as the revised preliminary responses to question 5(a) and 5(b).

July 18, 2013, preliminary responses to question 5(a) and 5(b)

5. Does the Agency agree that the overall clinical pharmacology program, including the planned clinical pharmacology studies and their proposed study designs, is sufficient to support the initial registration of RO5424802?

   FDA response: No. FDA recommends that Roche conduct the following studies in addition to the planned studies listed in Table 13 of the meeting background package during the development of RO5424802.

   a. A food effect study with the to-be-marketed drug product following the food effect guidance. per the FDA Guidance for Industry entitled "*Food-Effect Bioavailability and Fed Bioequivalence Studies*" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070241.pdf.

   b. A study to assess the effect of drugs known to alter the gastrointestinal pH (proton pump inhibitors, H2 antagonists and antacids) on the pharmacokinetics of RO5424802 as it demonstrates pH dependent solubility. The study may be conducted in a gated manner, first evaluating the effect of a proton pump inhibitors (PPIs) on the steady state exposure of RO5424802. In the event that concomitant administration of a PPI has a large impact on RO5424802 steady state exposure, H2 antagonists and antacids should be subsequently evaluated.

Revised preliminary responses to question 5(a) and 5(b).

Clinical Pharmacology

5. Does the Agency agree that the overall clinical pharmacology program, including the planned clinical pharmacology studies and their proposed study designs, is sufficient to support the initial registration of RO5424802?

   FDA response: No. FDA recommends that Roche conduct the following the studies in addition to the planned studies listed in Table 13 of the meeting background package during the development of RO5424802.

   a. A food effect study with the to-be-marketed drug product following the FDA Guidance for Industry entitled "*Food-Effect Bioavailability and Fed Bioequivalence Studies*" found at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070241.pdf.

b. A study to assess the effect of drugs known to alter the gastrointestinal pH (e.g., proton pump inhibitors, H_2 antagonists and antacids) on the pharmacokinetics of RO5424802 as it demonstrates pH dependent solubility. The study may be conducted in a gated manner, first evaluating the effect of a proton pump inhibitor (PPI) on the exposure of RO5424802. In the event that concomitant administration of a PPI has a large impact on RO5424802 exposure, H_2 antagonists and antacids should be subsequently evaluated.

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/s/

GINA M DAVIS
08/07/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 111723

GRANT –
BREAKTHROUGH THERAPY DESIGNATION

Hoffmann-La Roche Inc.
Attention: Jerald Grace, Pharm.D.
Program Manager, Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110

Dear Dr. Grace:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AF-802 (RO5424802).

We also refer to your May 1, 2013, request for Breakthrough Therapy designation. We have reviewed your request and have determined that AF-802 for the treatment of ALK-positive non-small cell lung cancer (NSCLC) patients who have progressed on crizotinib therapy meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of AF-802 for the treatment of ALK-positive NSCLC patients who have progressed on crizotinib therapy, including providing advice on generating evidence needed to support approval of the drug in an efficient manner. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA). A guidance document is currently under development.

In terms of next steps, please submit a Type B meeting request. This meeting will be for a multidisciplinary comprehensive discussion of your development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to the *Guidance for Industry: Formal Meetings between FDA or Sponsors and Applicants*[1] for procedures on requesting a meeting.

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf

If you have any questions, contact Gina Davis, Regulatory Project Manager, at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

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

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/s/

JOSEPH E GOOTENBERG on behalf of PATRICIA KEEGAN
06/26/2013

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208434

LATE-CYCLE MEETING MINUTES

Hoffmann-La Roche Incorporated
c/o Genentech, Inc.
Attention: Chung Ying Tao, Ph.D.
Associate Program Director, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080

Dear Dr. Tao:

Please refer to your New Drug Application (NDA) dated July 6, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Alecensa (alectinib) capsule, 150 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on November 20, 2015.

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

If you have any questions, call Gina Davis, Regulatory Project Manager at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Gideon Blumenthal, M.D.
Medical Officer, Cross Discipline Team Lead
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: November 20, 2015
Meeting Location: CDER WO 22 – Room 1311
Application Number: NDA 208434
Product Name: Alecensa (alectinib)
Applicant Name: Hoffmann-La Roche, Inc.
Meeting Chair: Gideon Blumenthal, M.D.
Meeting Recorder: Gina Davis, M.T.

FDA ATTENDEES

Division of Oncology Products 2 (DOP 2)
Patricia Keegan, M.D., Director, DOP 2
Gideon Blumenthal, M.D., Medical Team Lead, DOP 2
Erin Larkins, M.D., Medical Officer, DOP 2
Jennie Chang, PharmD., Clinical Analyst, OHOP/DOP 2
Gina Davis, M.T. Senior Regulatory Health Project Manager, DOP 2

Division of Hematology Oncology Toxicology (DHOT)
Whitney Helms, Ph.D., Nonclinical Supervisor, DHOT
Eias Zahalka, Ph.D., Nonclinical Reviewer, DHOT
Kimberly Ringgold, Ph.D., Nonclinical Reviewer, DHOT

Division of Biostatistics (DB V)
Huanyu (Jade) Chen, Ph.D., Statistical Reviewer, DB V
Kun He, Ph.D., Statistical Team Lead, DB V

Division of Clinical Pharmacology V (DCP V)
Stacy Shord, PhamD., Clinical Pharmacology Reviewer, DCP V
Hong Zhao, Ph.D., Clinical Pharmacology Team Lead, DCP V

Office of Product Quality (OPQ)
Olen Stephens, Ph.D., Branch Chief, OPQ

Office of Surveillance and Epidemiology (OSE)

Carolyn McCloskey, M.D, Medical Officer, OSE
Latonia Ford, BSN, MBA, Safety Regulatory Project Manager, OSE
Shaily Arora, Pharm,D., Pharmacovigilance Reviewer, OSE

APPLICANT ATTENDEES
Ali Zeaiter, M.D., Global Clinical Science Lead
Walter Borgdona, Ph.D., Senior Clinical Scientist
Bogdana Balas, M.D., Safety Science Lead
Sophie Golding, Ph.D., Project Lead Statistician
Peter Morcos, PharmD., Clinical Pharmacology Lead
Li Yu, Ph.D., Nonclinical DMPK Lead
Sven Kronenberg, Ph.D., Nonclinical Toxicology Lead
Christiane Froehlich, Ph.D., Technical Development Lead
Mireille Methlin Costantzer, PharmD, Global Regulatory Lead
Florence Tao, Ph.D., US Regulatory Partner
Chez Min Murdoch, US Regulatory Partner
Llorente Bonaga, Ph.D., Global Technical Regulatory Lead
Josina Reddy, M.D. Ph.D., Senior Group Medical Director
Nathan Winslow, Regulatory Franchise Director
Kin Tang, Ph.D., R.Ph., Technical Regulatory Group Director
Samir Megateli, Life Cycle Leader

APPLICANT SILENT LISTENERS
Sarah Lockwood, Ph.D., US Regulatory Associate
Anna Beryozkina, PharmD, US Regulatory Manager
Shailise Ross, Ph.D., US Regulatory Intern
Negar Sadrzadeh, Ph.D., US Technical Regulatory
Sandra Nino-Siddens, US Regulatory Team Leader
Kazuo Semitsu, US Labeling
Emily Bussiere, US Labeling
Lisa Kelsey, US Labeling
Mathias Schultz, Medical Science Director

1.0 BACKGROUND

NDA 208434 was submitted on July 6, 2015 for Alecensa (alectinib).

Proposed indication: The treatment of Treatment of ALK positive NSCLC.

PDUFA goal date: March 4, 2016

FDA issued a Background Package in preparation for this meeting on November 13, 2015.

2.0 DISCUSSION

1. Introductory Comments - 5 minutes: Welcome, Introductions, Ground rules, Objectives

   Discussion during the teleconference: Welcome, Introductions, Ground rules, Objectives addressed by Dr. Gideon Blumenthal.

   On November 13, 2015, the Division of Oncology Products 2, via the Late Cycle Meeting Agenda, proposed the following PMC to Hoffmann-La Roche (Roche).

   Postmarketing Commitment (PMC)

   - The Division is recommending a PMC to [redacted] (b) (4)

   Discussion during the teleconference: Roche will provide a response regarding the PMC and propose an alternative [redacted] (b) (4) before committing to the PMC. FDA acknowledged Roche's response and requested that the response be formally submitted as an amendment to the NDA.

2. Discussion of Substantive Review Issues

   Discussion during the teleconference: No discussion occurred as there are no substantive review issues.

3. Discussion of Minor Review Issues

   Discussion during the teleconference: No discussion occurred as there are no minor review issues.

4. Additional Applicant Data

   Discussion during the teleconference: No discussion occurred as Roche did not submit additional data.

5. Information Requests

   Discussion during the teleconference: An Information request was sent on November 18, 2015 and Roche provided a response on November 19, 2015. FDA was unable to provide feedback as the response was still under review by DMEPA.

6. Upcoming Advisory Committee Meeting

   Discussion during the teleconference: No discussion occurred as an Advisory Committee Meeting was not planned.

7. REMS or Other Risk Management Actions

Discussion during the teleconference: No discussion occurred as there are no REMS or Other Risk Management Actions associated with this application.

8. CMC Facilities

Discussion during the teleconference: FDA stated that the facilities inspection was not complete and anticipates completion in a few weeks. Roche requested FDA be more specific as to when the facilities inspection would be complete. FDA stated that additional information would be required before the CMC review could be complete (e.g. completion of Form 483). Roche acknowledged FDA's response and no additional discussion occurred.

9. Postmarketing Requirements (PMRs)/Postmarketing Commitments (PMCs)

Clinical

2995-1 Conduct and submit the results of at least one multicenter, randomized clinical trial establishing the superiority of alectinib over available therapy in patients with metastatic anaplastic lymphoma kinase positive non-small cell lung cancer (NSCLC).

Final Protocol Submission:	March 2014
Study/Trial Completion:	March 2019*
Final Report Submission:	June 2018**

*End of study, once the survival follow-up analysis is complete.
**CSR based on the primary endpoint, progression-free survival (PFS).

Clinical pharmacology

2995-2 Complete a pharmacokinetic trial to determine an appropriate dose of alectinib in patients with moderate to severe hepatic impairment.

Final Protocol Submission:	December 2015
Study/Trial Completion:	July 2017
Final Report Submission:	December 2017

Discussion during the teleconference: Roche acknowledged the two aforementioned PMRs and stated that milestone dates were provided on October 23, 2015.

10. Major Labeling Issues

The Alecensa (alectinib) label was discussed in great detail to include the sections listed below.

- Indication statement: inclusion of patients who are intolerant to crizotinib
- Section 6.1, Tables 3 and 4
- Section 14, Table 5: ORR and DoR by ITT
- Section 16, storage in the original container

Discussion during the teleconference: FDA requested Roche address the edits/changes to the Alecensa (alectinib) label and provide feedback. Roche acknowledged FDA's request and no further discussion occurred.

11. Review Plans

Discussion during the teleconference: Roche requested a time frame for approval of the Alecensa (alectinib) application. FDA stated that the plan was to approve before the end of the year. Roche acknowledged FDA's response and no discussion occurred.

12. Wrap-up and Action Items

Discussion during the teleconference: Roche will review the Alecensa (alectinib) label and provide feedback in a timely fashion.

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/s/

GIDEON M BLUMENTHAL
11/30/2015

MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 10, 2015
TIME: 12:00 PM – 1:00PM
LOCATION: CDER WO 22- Room 4266
APPLICATION: NDA 208434
DRUG NAME: Alecensa (alectinib)
TYPE OF MEETING: Late Cycle Meeting – Internal Meeting
MEETING CHAIR: Patricia Keegan, M.D.
MEETING RECORDER: Gina Davis

FDA ATTENDEES:
Patricia Keegan, Patricia, Division of Oncology Products 2
Gideon Blumenthal, Division of Oncology Products 2
Erin Larkins, Division of Oncology Products 2
Gina Davis, Division of Oncology Products 2
Leslie Doros, Division of Oncology Products 2
Whitney Helms, Division of Hematology Oncology Toxicology
Eias Zahalka, Division of Hematology Oncology Toxicology
Stacy Shord, Division of Clinical Pharmacology V
Hong Zhao, Division of Clinical Pharmacology V
Huanyu (Jade) Chen, Division of Biostatistics V
Olen Stephens, Division of New Drug Quality Assessment
Rajiv Agarwal, Division of New Drug Quality Assessment
Carolyn McCloskey, of Surveillance and Epidemiology
Grace Jones, Office of Surveillance and Epidemiology
Latonia Ford, Office of Surveillance and Epidemiology

BACKGROUND:

On July 6, 2015, Hoffmann-La Roche (Roche) submitted a New Drug Application (NDA) to the Division of Oncology Products 2 (DOP 2) for their product Alecensa (alectinib) for the treatment of ALK Positive NSCLC. This meeting was scheduled to review the agenda and Late Cycle Meeting Package that will be sent to Roche in preparation for the November 20, 2015, Late Cycle Meeting (LCM).

MEETING OBJECTIVES:

- Identify any key issues that will be discussed at the LCM.

DISCUSSION POINTS:

- No substantive review issues, no risk management actions, and no plans for an Advisory Committee meeting are associated with this application.

- In an electronic (email) communication, dated November 6, 2015, Roche requested that their counter-proposal to the Alecensa (alectinib) package insert be discussed during a teleconference prior to the November 20, 2015, face to face LCM. Those issues are listed below;

    - Indication statement: inclusion of patients who are intolerant to crizotinib
    - Section 14, Table 5: ORR and DoR by ITT
    - Section 16, storage in the original container

- [redacted] (b) (4)

DECISIONS (AGREEMENTS) REACHED:

The following topics will be discussed in detail at the LCM;

- Roche's counter-proposal to the Alecensa (alectinib) label
- [redacted] (b) (4)

ACTION ITEMS:

- DOP 2 will send the LCM Package to the Roche on or before Friday, November 13, 2015.

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/s/

GINA M DAVIS
11/13/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208434

LATE CYCLE MEETING
BACKGROUND PACKAGE

Hoffmann-La Roche Incorporated
c/o Genentech, Inc.
Attention: Chung Ying Tao, Ph.D.
Associate Program Director, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080

Dear Dr. Tao,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alecensa (alectinib) capsule, 150 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for November 20, 2015. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Gina Davis, Senior Regulatory Health Project Manager, at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: November 20, 2015 – 12:00 PM- 1:00 PM
Meeting Location: CDER WO 22 – Room 1311
Application Number: NDA 208434
Product Name: Alecensa (alectinib)
Indication: Treatment of ALK positive NSCLC
Sponsor/Applicant Name: Hoffmann-La Roche, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

There are no substantive review issues at this time.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes: Welcome, Introductions, Ground rules, Objectives

2. Information Requests –Proposed Postmarketing Commitment (PMC)

   - The Division is recommending a PMC to (b) (4)

3. Postmarketing Requirements (PMR)

   On October 14, 2015, the proposed PMRs, listed below, were discussed with Hoffmann-La Roche (Roche) and milestone dates were requested on or before October 31, 2015. Roche provided milestone dates on October 23, 2015.

   Clinical

   2995-1 Conduct and submit the results of at least one multicenter, randomized clinical trial establishing the superiority of alectinib over available therapy in patients with metastatic anaplastic lymphoma kinase positive non-small cell lung cancer (NSCLC).

   Final Protocol Submission March 2014
   Study/Trial Completion: March 2019*
   Final Report Submission: June 2018**

   *End of study, once the survival follow-up analysis is complete.
   **CSR based on the primary endpoint, progression-free survival (PFS).

   Clinical pharmacology

   2995-2 Complete a pharmacokinetic trial to determine an appropriate dose of alectinib in patients with moderate to severe hepatic impairment.

   Final Protocol Submission December 2015
   Study/Trial Completion: July 2017
   Final Report Submission: December 2017

4. CMC – Facilities

CMC facilities - still pending.

5. Major labeling issues

Package Insert

On Monday, November 9, 2015, Roche sent an electronic (email) communication requesting a teleconference, prior to the Late Cycle Meeting, to discuss the following issues regarding the Alecensa (alectinib) label.

- Indication statement: inclusion of patients who are intolerant to crizotinib
- Section 14, Table 5: ORR and DoR by ITT
- Section 16, storage in the original container (further comments below)

These issues will be addressed at the Late Cycle Meeting.

6. Review Plans – 5 minutes

7. Wrap-up and Action Items – 5 minutes

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/s/

PATRICIA KEEGAN
11/13/2015