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APPLICATION NUMBER:

208434Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	December 9, 2015
From	Patricia Keegan
Subject	Division Director Summary Review
NDA #	NDA 208434
Applicant	Hoffmann-La Roche Inc.
Date of Submission	July 6, 2015
PDUFA Goal Date	March 4, 2016
Proprietary Name / Non-Proprietary Name	Alecensa/ alectinib
Dosage Form(s) / Strength(s)	capsules for oral administration/150 mg
Applicant Proposed Indication(s)	Alecensa is indicated 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.
Recommended Action for NME:	Approval
Recommended Indication	ALECENSA is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive, metastatic non-small cell lung cancer (NSCLC) who have progressed on, or are intolerant to crizotinib. This indication is approved under accelerated approval based on tumor response rate and duration of response *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager	Gina Davis
Medical Officer Review	Erin Larkin
Statistical Review	Huanyu (Jade) Chen
Pharmacology Toxicology Review	Eias Zahalka & Kimberly Ringgold
OPQ Review	Olen Stephens (Application Team Lead); Charles Jewell (Drug Substance); Rajiv Agarwal (Drug Product & EA Assessment); Zhaoyang Meng (Microbiology & Process); Zhong Li (Facility); Gerlie Gieser (Biopharmaceutics)
Clinical Pharmacology Review	Stacy S. Shord; Jingyu (Jerry) Yu; Ping Zhao
OPDP Review	Nazia Fatima
OSI Review	Lauren Iacono-Connors
OSE/DMEPA Review	Grace P. Jones
OSE/DRISK Review	Mona Patel
DPMH Review	Suchitra M. Balakrishnan
Patient Labeling Review	Rowell Medina & Nazia Fatima
Associate Director for Labeling Review	Jennie Chang
CDTL Review	Gideon Blumenthal

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DPMH=Division of Pediatric and Maternal Health

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Metastatic, anaplastic lymphoma kinase (ALK) mutation-positive, non-small cell lung cancer (NSCLC) is genetically distinct form of lung cancer that is not curable with available therapy. Based on the National Institute of Health (NIH) Surveillance, Epidemiology and End Results (SEER) Program, an estimated 9, 400 patients were expected to be diagnosed with ALK mutation-positive NSCLC in 2015. Crizotinib, which is indicated the treatment of patients with metastatic NSCLC whose tumors are ALK-positive as detected by an FDA-approved test, is the current first-line therapy administered in such patients, however acquired resistance to crizotinib develops, usually after several months of treatment. The median survival in patients with metastatic ALK mutation-positive NSCLC was 20.8 months in patients receiving crizotinib as first-line therapy, thus confirming the life-threatening nature of this subtype of NSCLC.

Alectinib is the second kinase inhibitor with a broader spectrum of activity against multiple ALK mutations that has demonstrated durable objective responses in patients with ALK mutation-positive NSCLC whose disease had progressed on crizotinib therapy, likely due to development of additional mutations in ALK and/or other genes. Although not directly compared in a randomized clinical trial, 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. Demonstration of the treatment effect was descriptive; however it meets the criteria for substantial evidence of a treatment effect as the results are similar in two separate, multicenter trials (Studies NP28761 and NP28673). These trials that 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. These data are further supported by evidence of clinically meaningful ORR in the subset of 110 patients enrolled in Study NP29763 who had progressed on crizotinib and received prior platinum-based chemotherapy, where the ORR was 39% (95% CI: 30, 49) and the median duration of response was 10.9 months. In addition, there was evidence of antitumor activity in central nervous system (CNS) metastases, a common site of metastases and disease progression where effective drug delivery across the blood brain barrier is likely to impact tumor control. Among patients identified by the independent review committee as have measurable CNS disease, the CNS response rate (per RECIST) was 57% (95% CI: 39%, 74%) with median durations of CNS response of 9.1 months in Study NP28673 and the ORR was 69%

(95% CI: 41%, 89%), where the median duration of response was not estimable, in Study NP28761.

The clinical safety experience is very limited (253 patients), thus uncommon serious adverse reactions, occurring at an incidence of ≤1%, may be identified in the post-marketing setting. However, based on the current data, the risks of alectinib are qualitatively similar to that occurring with other FDA-approved drugs in this class (ALK inhibitors) or with other anti-neoplastic agents approved for treatment of NSCLC. The most common adverse reactions of alectinib were fatigue (41%), constipation (34%), edema (30%) and myalgia (29%). Across both trials, 23% required at least one dose reduction for adverse reactions with a median time to first dose reduction of 48 days. The most common adverse reactions resulting in dose reductions or interruptions of dosing were hyperbilirubinemia (6%), elevated CPK levels (4.3%), elevated ALT levels (4.0%), elevated AST levels (2.8%), and vomiting (2.8%). The incidence of serious adverse reactions requiring dose modifications is approximately 23%, which is not unusual for anti-neoplastic agents. Dose modifications were generally successful in the management of serious, including fatal, adverse reactions of hepatotoxicity, ILD, severe myalgia and CPK elevation, and bradycardia. The serious risks of alectinib are qualitatively similar and not substantially higher in incidence than those observed with other products in the class (crizotinib and ceritinib) or other antineoplastic agents, which based on post-marketing experience, can be safely administered without REMS.

The effect of alectinib on durable objective response rate has been demonstrated and is numerically better than that achievable with FDA-approved therapy. Based on prior experience with crizotinib, an effect on ORR of sufficient magnitude and duration is likely to predict an effect on progression-free survival. The risks of alectinib are acceptable in this patient population, where the potential for an improvement in a median survival for less than 2 years would be considered to outweigh risks that can be generally managed with dose modification. Therefore, I have concluded the risk:benefit profile is favorable and recommend approval of alectinib with the agreed-upon labeling and post-marketing requirements.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of 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	Metastatic, ALK mutation-positive, non-small cell lung cancer is genetically distinct form of lung cancer that is not curable with available therapy.

[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. Accessed on December 5, 2015.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	annually. Eleven distinct fusion proteins involving ALK have been identified in NSLCL; rearrangement of the echinoderm microtubule-associated protein-like 4 (EML4)-ALK is the predominant ALK fusion in lung cancer.[3] ALK mutation-positive NSCLC has both distinct clinical and pathologic characteristics, occurring at a younger median age and in non-smokers and females more commonly than in those with NSCLC without ROS-1, RET, or ALK mutations. Patients with ALK mutation-positive lung cancers are more likely to have extracellular mucin, cribriform pattern, signet ring cells and hepatoid cytology on pathologic evaluation.[1] There is no evidence that the presence of ALK mutations confer a better prognosis.[4] [5] 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] and median survival of 20.8 for those receiving crizotinib as second-line therapy and compared with reported median survivals of 9.1 months with docetaxel alone or 10.5 months with docetaxel and ramucirumab.[6,7] While there are no good estimates of the estimated 5-year survival rate of patients with metastatic, ALK mutation-positive NSCLC, available therapy indicates that the disease is not curable, thus there remains an unmet need for this life-threatening form of cancer.	

[3] *ALK* in Lung Cancer: Past, Present, and Future. Shaw AT and Engelman JA. Clin Oncol 31(8): 1105–1111, 2013.
[4] *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.
[5] 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.
[6] http://www.accessdata fda.gov/drugsatfda_docs/label/2015/202570s014lbl.pdf
[7] http://www.accessdata fda.gov/drugsatfda_docs/label/2015/125477s011lbl.pdf

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	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. • Similarly, pembrolizumab was approved for the treatment of PD-L1 positive NSCLC under the provisions of 601 Subpart E and is not considered available therapy for this patient population as clinical benefit has not been verified. 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.[8]	There are no drugs with regular FDA approval for the treatment of patients with ALK-mutation- positive NSCLC who are no longer responding to or are intolerant of crizotinib

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• 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.	
Benefit	In two single-arm, multicenter trials, treatment with alectinib 600 mg orally twice daily demonstrated an overall response rate (ORR) of 44% (95% CI: 36%, 53%) and 38% (95% CI: 28%, 49%) with a 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. Among the 110 patients enrolled in Study NP29763 who had progressed on crizotinib and received prior platinum-based chemotherapy, there were 43 patients who achieved a partial response, for an ORR of 39% (95% CI: 30, 49) and a median duration of response 10.9 months. In addition, to the overall response rate, evidence of reduction in central nervous system (CNS) tumor burden was also observed, with a CNS response rate as determined by independent review (per RECIST) in patients with measurable CNS metastases at study entry of 57% (95% CI: 39%, 74%) with a median duration of CNS response of 9.1 months in Study NP28673 (n=35) and 69% (95% CI: 41%, 89%) where the median duration of response was not estimable, in Study NP28761 (n=16).	Based on the data provided in this NDA, alectinib provides a clinically meaningful improvement in durable overall response rate as compared to the FDA-approved therapies for the second-line treatment of NSCLC (nivolumab, docetaxel alone or with ramucirumab, and pemetrexed), including the subset of patients in Study NP28673 (n=110) receiving third-line therapy for ALK mutation positive NSCLC. Based on clinical trials in the first-line setting with another ALK inhibitor (crizotinib), an improvement in ORR and duration of response over available therapy [platinum-based chemotherapy] was subsequently shown to lead to clinically important improvements in progression-free survival.
Risk	The clinical safety experience is very limited (253 patients), thus uncommon serious adverse reactions, occurring at an incidence of ≤1%, may be identified in the post-marketing setting. The most common adverse reactions of alectinib were fatigue (41%),	The risks of alectinib are qualitatively similar to that occurring with other FDA-approved drugs in this class (ALK inhibitors) or with other anti-neoplastic agents approved for treatment of NSCLC. The incidence of serious

[8] http://www.accessdata fda.gov/drugsatfda_docs/label/2015/125477s011lbl.pdf

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	constipation (34%), edema (30%) and myalgia (29%). Across both trials, 23% required at least one dose reduction for adverse reactions with a median time to first dose reduction of 48 days. The most common adverse reactions resulting in dose reductions or interruptions of dosing were hyperbilirubinemia (6%), elevated CPK levels (4.3%), elevated ALT levels (4.0%), elevated AST levels (2.8%), and vomiting (2.8%). Fatal adverse reactions occurred in 2.8% of the 253 patients enrolled in Studies NP28761 and NP28673; these fatal events were hemorrhage (0.8%), intestinal perforation (0.4%), dyspnea (0.4%), pulmonary embolism (0.4%), and endocarditis (0.4%); however, as there is no comparator arm, it is difficult to place these fatal adverse reactions in the context of the disease setting. The most serious adverse reactions of alectinib are hepatotoxicity, interstitial lung disease, muscular toxicity manifesting as increased in CPK and severe myalgia, and bradycardia. Other areas of concern, which did not present as serious adverse reactions in Studies NP28761 and NP28673, are photosensitivity and visual defects, but which would be of concern if it occurred at a greater severity.	adverse reactions requiring dose modifications is approximately 23%, which is not unusual for anti-neoplastic agents. Dose modifications were generally successful in the management of serious, including fatal, adverse reactions of hepatotoxicity, ILD, severe myalgia and CPK elevation, and bradycardia.
Risk Management	The NDA did not contain proposed Risk Evaluation and Mitigation Strategies (REMS). Hoffmann-La Roche proposed to manage risks through product labeling and routine post-marketing surveillance.	The serious risks of alectinib are qualitatively similar and not substantially higher in incidence than those observed with other products in the class (crizotinib and ceritinib) or other antineoplastic agents, which based on post-marketing experience, can be safely administered without REMS.

2. Background

On July 18, 2011, a pre-IND meeting was held to discuss the development program for alectinib (also known as AF802 and CH5424802) for the treatment, as a single agent, of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with the *ALK* translocation. The sponsor, Chugai, proposed to contained a dose-finding and activity estimating trial of alectinib in patients with ALK-positive NSCLC with progression after crizotinib therapy and one or more chemotherapy regimens. Chugai noted that an ongoing dose-finding and activity estimating trial (AF-001JP) was being conducted in Japan in patients with *ALK* fusion NSCLC who had progressed following chemotherapy but were ALK inhibitor-naïve. FDA advised that for studies intended to support an NDA, patient selection be based on detection of ALK by an FDA-approved test. With regard to use of data from single arm trials to support accelerated approval, FDA stated that an ORR of (b)(4)% would not be sufficient to support such a request. FDA further advised that the size of the safety database necessary to support an NDA should be discussed after preliminary efficacy data were available. Advice regarding clinical pharmacology studies necessary to support drug development and an NDA were also provided.

On September 30, 2011, IND 111723 was submitted to the FDA and was allowed to proceed on October 28, 2011. In the "May Proceed" communication, FDA requested additional information on product manufacturing and advice on the clinical pharmacology development program.

On December 21, 2012, FDA acknowledged transfer of the IND from Chugai Pharma USA, LLC to Hoffman-La Roche, Inc.

On June 26, 2013, FDA designated alectinib as a Breakthrough Therapy for the treatment of patients with ALK-positive NSCLC that had progressed on crizotinib therapy

On July 22, 2013, an interdisciplinary BTD meeting was held to discuss the proposed patient population and analysis of patients enrolled in Studies NP28761and 28763 to support a request for accelerated approval based on demonstration of durable ORR and the general design of a confirmatory trial (randomized (1:1), multicenter, active-controlled, open-label study (Study BO28984) to compare alectinib with crizotinib in patients with advanced ALK rearrangement-positive NSCLC who were treatment-naive or had received one line of standard platinum-based chemotherapy). Key discussion items and agreements were:

- FDA agreed that results from Studies NP28761 and NP28673 enrolling 250 patients treated at the RP2D dose to be marketed in the United States, supported by data from 70 patients from Study AF-001JP in the pooled safety database, can potentially permit a substantive review for accelerated approval.
- FDA agreed with the definition for "crizotinib failure" as patients with disease progression based on RECIST criteria, version 1.1, within 60 days of the last dose of crizotinib.
- FDA stated that Roche's proposal to modify the protocol to target an overall response rate of 50% with the lower bound of 35% was acceptable. However, whether the estimated

ORR and accompanying confidence interval was sufficient to support a request for accelerated approval would be a review issue.

- FDA raised no objections to the design of the proposed confirmatory trial.
- FDA encouraged Roche to request a meeting to discuss the clinical development plan for RO5424802 (b) (4) 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)
- FDA did not agree (b) (4) FDA strongly recommended (b) (4) FDA agreed to continue discussions on the acceptability on the proposed formulation for commercial marketing based on additional data to be submitted (b) (4)

On October 23, 2013, a meeting was held to discuss CMC issues and continue discussion of data necessary to support the proposed SLS content in the product intended for commercial use. Agreement was reached on the design of the relative bioavailability study over a range of SLS concentrations.

On November 14, 2013, a meeting was held to reach agreement on the trial design (b) (4)

On December 12, 2013, a meeting was held to discuss the design of the proposed confirmatory trial, Study BO28984, intended to verify the clinical benefit of alectinib and to support the proposed indication for "the treatment of adults with advanced non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive, (b) (4) ."

On August 6, 2014, an intermediate-size expanded access protocol was submitted; after responding to information requests from FDA and incorporating requested modifications, the trial was allowed to proceed on December 3, 2015.

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 an 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, ≥ 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, the Office of Orphan Drug Products designed alectinib as an orphan drug for the treatment of ALK-positive non-small cell lung cancer.

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 [redacted] testing in the NDA.
- Roche agreed to provide data that demonstrates that the variability observed in [redacted] 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.

On April 7, 2015, a pre-NDA meeting was held to reach final agreement on the content and format of the planned NDA, focusing primary on clinical issues.

- 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, but not in patients with locally advanced ALK-positive NSCLC, as data are limited.
- The proposed clinical experience was sufficient to characterize safety with the proposed formulation to be marketed.
- FDA stated that the studies were inadequate in design [redacted]
- FDA stated that the new data cut-off date of January 8, 2015, for efficacy results from Study NP28673 was acceptable.
- FDA agreed to the proposed schedule for submission of a rolling NDA, proposed content and structure of clinical datasets, proposal for submission of CRFs and case narratives.
- Hoffmann-La Roche agreed to provide a flag in datasets for patients who discontinued crizotinib for adverse reactions or for progressive disease and to provide data on the interval between last dose of crizotinib and first dose of alectinib in clinical datasets.

3. Product Quality

I concur with the conclusions of the product quality review team that there are no chemistry, manufacturing, and control issues that preclude approval of this NDA. The Office of Process and Facilities recommends approval of the manufacturing and testing sites based on inspectional findings. There are no post-marketing commitments identified to address product quality issues in the post-marketing setting.

Alectinib hydrochloride, the drug substance, is white to yellow white powder that has low solubility in aqueous solutions, slightly hydroscopic, and photolabile. Alectinib drug product is manufactured using conventional equipment and manufacturing processe [redacted] The acceptability of the SLS concentration was supported by relative bioavailability studies demonstrating that [redacted]% SLS was necessary to achieve relative bioavailability to the product administered in clinical trials, nonclinical toxicology studies, and comparability to the product administered in clinical trials supporting approval of this NDA. Alectinib will be marketed as an immediate-release capsule as a single strength (150 mg alectinib free base). An expiration period of 24 months is granted when

stored in 250 mL round, 240-count white HDPE bottles with child resistant closures when stored below 30 ^{O}C and protected from light.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions of the nonclinical pharmacology/toxicology review team that there are no nonclinical issues that preclude approval of this NDA.

The NDA contained the results of nonclinical in vitro and in vivo pharmacology studies supporting proposed mechanism of action of alectinib as a reversible inhibitor of the ALK and the re-arranged during transfection (RET) kinases at concentrations achieved with the recommended dose, with suppression of ALK phosphorylation.

The nonclinical, 13-week toxicology studies conducted in rats and monkeys were considered relevant based on evidence that the metabolism, distribution, protein binding, and elimination of alectinib were similar to that observed in humans. The concentrations of the alectinib and the major active metabolite (M4) in rats exceeded those achieved with the recommended human dose and in monkeys were approximately half those achieved in humans. Toxicities observed in animals were qualitatively similar to those observed in humans, with pathologic findings in the adrenal gland, gastrointestinal (GI) tract, liver, reproductive system (testes, epididymis, seminal vesicles, and prostate) and respiratory system (lung and trachea). In addition, toxicology studies in rats revealed adverse effects on teeth and growing bones, which were considered potentially relevant to the pediatric population (and thus described in Section 8.4 of product labeling), but not for the indicated population, as ALK-positive NSCLC occurs only in adults. Clinical findings included evidence of hemorrhage in the GI tract and intestinal perforation. Clinical laboratory findings included increases in creatinine, cholesterol, triglyceride, alkaline phosphatase isoenzymes, increases in reticulocytes, platelets, and neutrophils, decreases in hematocrit and hemoglobin, and increased APTT and PT in rats.

Since toxicology studies were conducted with a preparation of alectinib that contained no SLS, a 28-day bridging study was performed, to evaluate the toxicology of the to-be-marketed alectinib containing (b) (4)% SLS. This study showed comparable systemic exposure and toxicity profiles to that achieved with the alectinib formulation used in 13-week animal studies.

Safety pharmacology studies and nonclinical studies demonstrated hypotension and bradycardia, which have been observed in clinical studies, but no evidence of QT prolongation and a negative hERG assay. Evidence of phototoxicity (also observed in clinical studies) was demonstrated in a cytotoxicity assay model.

Alectinib is clastogenic in the micronucleus assay with an increase in the chromosome number but was not mutagenic. Pilot embryofetal toxicology studies demonstrated embryofetal toxicity and maternal toxicity at exposures of 2.9-fold and 2.7-fold, in rabbits and rats respectively, compared with exposures achieved with the recommended human dose. Effects included fetal loss and low fetal weight in species, dilated ureter, thymic cord, small ventricle and thin ventricle wall, and reduced number of sacral and caudal vertebrae in rats, and retroesophageal subclavian artery in rabbits. Since ALK signaling appears to be important in early neurologic

development, this potential concern was noted in product labeling. Based on the positive findings in these pilot studies, further embryofetal development studies were not required. In addition, based on the proposed indication and current 5-year survival rates, carcinogenicity studies and fertility studies were not required.

5. Clinical Pharmacology

I concur with the conclusions of the clinical pharmacology reviewers that there are no outstanding clinical pharmacology issues that preclude approval and that the proposed dosage regimen of 600 mg orally, twice daily, taken with food is supported by the clinical pharmacology studies. A post-marketing study is required to evaluate and identify a reasonably safe dose of alectinib in patients with moderate or severe hepatic impairment. In addition, the clinical pharmacology reviewers requested that the results of clinical pharmacokinetic trials evaluating the effect of alectinib on the pharmacokinetics of a sensitive multidrug resistance protein 1 (MDR1) substrate and a sensitive breast cancer resistance protein substrate be submitted to the IND when completed.

The NDA contained the results of eight clinical pharmacology studies (a relative bioavailability and bioequivalence study with capsules with different percentages of SLS, a mass balance study, drug interaction studies with CYP inducers and inhibitors, drug interaction study with pH inhibitor, clinical pharmacology data obtained in Studies NP28761 and NP28673. In addition, the NDA contained the results of a population pharmacokinetic (popPK) analysis, E-R analyses for efficacy and safety, and physiological based pharmacokinetic (PBPK) analyses for drug interactions and food effect.

As noted, the proportion of patients requiring dose modification for adverse reactions was 23%, indicating that the majority of patients are able to tolerate the proposed dosage regimen. There was no exposure–response (E-R) relationship identified for efficacy (best overall response) or toxicity (grade 3 or higher adverse events or other clinically significant adverse events) among patients receiving alectinib 600 mg BID, supporting the dosage regimen.

Alectinib exhibits dose-proportional pharmacokinetics over the dose range of 400 to 600 mg BID and both alectinib and its major active metabolite (M4) are bound to human plasma proteins (>99%). The absolute bioavailability of alectinib is 37% under fed conditions in healthy subjects. Alectinib reached maximal concentrations after approximately 4 hours and exhibited a geometric mean elimination half-life of 32 hours for alectinib and 31 hours for M4 following administration of alectinib at the recommended dose in patients with ALK-positive NSCLC. The dosing schedule of twice daily dosing was selected to avoid an increased incidence of higher adverse reactions at the maximal concentrations which would be achieved following a single daily dose of 1200 mg; based on its half-life, there is no need to make up missed doses of alectinib.

There was a clinically significant effect on alectinib exposure when taken with or without food. In a food effects study conducted in 18 healthy volunteers receiving a single dose, the individual and combined exposures of alectinib and of M4 (the major active metabolite) were

increased by approximately 3-fold higher when alectinib was taken with a high-fat meal compared to those when alectinib was taken under a fasted state. Clinical studies supporting efficacy directed patients to take alectinib with food and this recommendation has been included in product labeling. There were no clinically important effects of concurrent administration of pH inhibitors on the pharmacokinetics of alectinib or M4.

In mass balance studies, the liver appears to be the major elimination pathway with 98% of a radiolabeled dose eliminated in the feces. Both alectinib and its major active metabolite, M4, are metabolized by CYP3A4. However, based on drug interaction studies conducted with alectinib and either rifampin or posoconazole, no dose adjustment is needed for patients taking a CYP3A4 modulator.

Based on the population pharmacokinetic (popPK) analysis, no dose adjustment of alectinib is needed in patients based on age, gender, body weight, mild hepatic impairment, mild to moderate renal impairment (CLcr 30 to 89 mL/min), or race (White, Asian and Other). The pharmacokinetics of alectinib and of M4 have not been studied in patients with severe renal impairment, end-stage renal disease or moderate to severe hepatic impairment. Since alectinib is primarily metabolized by the liver, a post-marketing study is required to assess the pharmacokinetics and provide recommendations on a reasonably safe dose of alectinib in patients with moderate or severe hepatic impairment but were not required for renal impairment based on the lack of effects on pharmacokinetics in patients with mild to moderate renal impairment and the minor role, if any, of renal metabolism of alectinib.

Based on serial ECGs obtained in 221 patients receiving alectinib at the recommended dose, there was no evidence of a clinically important increase in QTc.

6. Clinical Microbiology

There were no clinical microbiology data submitted in this NDA; review of quality sterility issues are discussed in section 3 of this review.

7. Clinical/Statistical-Efficacy

I concur with the conclusions of the statistical and clinical review team that there are no outstanding clinical efficacy issues that preclude approval of this NDA. Furthermore, I have concluded that the NDA contains substantial evidence of a treatment effect on overall response rate that is durable and that the durable response rates in these two single arm trials represent a clinically meaningful improvement in ORR over available therapy (i.e., docetaxel alone or with ramucirumab, pemetrexed, and nivolumab).

The data from the clinical studies supporting this NDA were considered reliable based on bioresearch monitoring inspections of two clinical study sites, selected for high rates of accrual to one or both studies, and of the NDA sponsor.

Both Study NP28761 and NP28673 were open-label, multicenter, two part trials, consisting of an initial dose-finding, safety and tolerability portion and a fixed dose, activity-estimating portion conducted at the recommended Phase 2 dose. Both studies were amended several times with regard to patient eligibility and analysis plan, among other aspects. For the

purposes of this NDA, the version of the protocol and agreements reached on the patient subpopulation and analysis of each study and pooled analyses of CNS response characteristics are based on the agreements reached during the July 22, 2013, and September 30, 2104 meetings with FDA.

In Study NP28761, the initial portion of the study explored the safety of alectinib at doses of 300 mg twice daily (BID) under fed and fasting conditions, and 460, 600,760, and 900 mg BID under fed conditions; this was followed by an activity-estimating portion in which patients received alectinib at the recommended Phase 2 dose (600 mg orally BID). Key eligibility criteria for the second portion of the study were locally advanced or unresectable ALK-positive NSCLC and disease progression during crizotinib treatment or intolerance of crizotinib; patients were permitted to have received prior chemotherapy but this was not required.

In Study NP28673, the initial portion of the study explored the safety of alectinib at doses of 600 mg and 900 mg BID under fed conditions, followed by the fixed-dose activity-estimating portion of the study, in which patients received alectinib at the recommended Phase 2 dose (600 mg BID). Key eligibility criteria for the second portion of the study were a diagnosis of unresectable, locally advanced (AJCC Stage IIIB) or metastatic NSCLC and documented ALK rearrangement as determined by an FDA-approved test; the trial permitted enrollment of patients with disease progression following prior crizotinib and patients who had not received an ALK inhibitor.

The analysis plan for Study NP28761, as revised and discussed at the July 22, 2013 BTD meeting was to enroll 85 patients treated at the recommended Phase 2 dose. Assuming that the true ORR was 65%, then 85 patients were 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.

The analysis plan for Study NP28673, as revised and discussed at the July 22, 2013 BTD meeting was to enroll 85 patients who received prior chemotherapy and progressed on crizotinib treated at the recommended Phase 2 dose. The assumptions and power calculations were similar to those for Study NP28761. In addition, Study NP28673 would enroll an additional, "unpowered" cohort of 45 patients who were chemotherapy-naïve.

Results:

Study NP28761 was conducted at 27 centers within North America (26 sites in US and 1 in Canada) and enrolled 87 patients in the activity-estimating portion of the trial who had disease progression following crizotinib. Baseline demographic and disease characteristics were median age 54 years old (range 29 to 79, 18% were 65 and over), 84% White and 8% Asian, 55% female, 35% ECOG PS 0 and 55% ECOG PS 1, 100% never or former smokers, 99% Stage IV, 94% adenocarcinoma, and 74% prior chemotherapy. The most common sites of extra-thoracic metastasis included 60% CNS (of whom 65% had received CNS radiation), 43% lymph nodes, 36% bone, and 34% liver.

Study NP28673was conducted internationally and enrolled 138 patients in the activity-estimating portion of the trial who had disease progression on or following crizotinib or who were unable to tolerate crizotinib. Baseline demographic and disease characteristics were median age 52 years old (range 22 to 79, 10% were 65 and over), 67% White and 26% Asian, 56% female, 32% ECOG PS 0 and 59% ECOG PS 1, 98% never or former smokers, 99% Stage IV, 96% adenocarcinoma, and 80% prior chemotherapy. The most common sites of extra-thoracic metastasis included 61% CNS (of whom 73% had received CNS radiation), 51% bone, 38% lymph nodes, and 30% liver.

The median duration of follow-up on Study NP28761 was 4.8 months for both IRC and Investigator assessments and on Study NP28673, 10.9 months for IRC assessment and 7.0 months for Investigator assessment. All responses were partial responses. The efficacy results for Studies NP28761 and NP28673 are summarized in the table below, abstracted from the USPI.

Efficacy Analyses in Studies NP28761 and NP28673				
Efficacy Parameter	**Study NP28761 (N=87)**		**Study NP28673 (N=138)**	
	IRC* Assessment	**Investigator Assessment**	**IRC* Assessment**	**Investigator Assessment**
Objective Response Rate (95% CI)	38% (28; 49)	46% (35; 57)	44% (36; 53)	48% (39; 57)
Number of Responders	33	40	61	66
Median Duration of Response (months); (95% CI)	7.5 (4.9, NE)	NE (4.9, NE)	11.2 (9.6, NE)	7.8 (7.4, 9.2)

Pooled Analysis of CNS ORR and Duration of Response in Patients with Measurable CNS Lesions at Entry	
Efficacy Parameter	**N=51**
CNS Objective Response Rate (95% CI)	61% (46, 74)
Complete Response	18%
Partial Response	43%
Median Duration of CNS Response (months (95% CI)	9.1 (5.8, not evaluable)

Among the 110 patients enrolled in Study NP28673 who had progressed on crizotinib and received prior platinum-based chemotherapy, there were 43 patients who achieved a partial response, for an ORR of 39% (95% CI: 30, 49) and a median duration of response 10.9 months.

In response to FDA's request for information regarding the safety and efficacy of administration of alectinib to patients who were intolerant of crizotinib, data on 5 such crizotinib-tolerant patients receiving alectinib across the clinical development program were submitted. These data supported the conclusion that patients unable to tolerate crizotinib due to hepatotoxicity or pulmonary toxicity/pneumonitis, could tolerate alectinib. In four of these 5 patients, the investigator identified partial responses were observed with median durations of 2.8, 2.8, 12.8+, and 15.4 months.

8. Safety

Adequacy of drug exposure experience and clinical safety assessments
The size of the safety database for assessment of the toxicity of alectinib (253 patients enrolled in one of two single arm, multicenter trials with a median duration of exposure of 9.3 months and where 100 patients were exposed to alectinib for more than one year), was suboptimal,and further limited by assessment at a single dosage regimen (600 mg per day). However, the ability to detect serious adverse reactions occurring in ≥ 1.5% of patients was considered sufficient given the life-threatening nature of relapsed/refractory ALK mutation-positive NSCLC to conduct a risk:benefit assessment. The clinical protocols contained adequate monitoring for adverse reactions predicted by clinical experience with other drugs in this class (ALK kinase inhibitors) or by nonclinical studies conducted with alectinib.

Major safety concerns
Fatal adverse reactions occurred in 2.8% of the 253 patients enrolled in Studies NP28761 and NP28673; these fatal events were hemorrhage (0.8%), intestinal perforation (0.4%), dyspnea (0.4%), pulmonary embolism (0.4%), and endocarditis (0.4%). Alectinib treatment was terminated for adverse reactions in 6% of patients; the most common adverse reactions leading

to discontinuation of alectinib were hyperbilirubinemia (1.6%), increased ALT levels (1.6%), and increased AST levels (1.2%). Across both trials, 23% required at least one dose reduction for adverse reactions with a median time to first dose reduction of 48 days. The most common adverse reactions resulting in dose reductions or interruptions of dosing were hyperbilirubinemia (6%), elevated CPK levels (4.3%), elevated ALT levels (4.0%), elevated AST levels (2.8%), and vomiting (2.8%).The following major safety concerns were identified during review of this NDA and are described in the Warnings and Precautions section of product labeling:

- Hepatic toxicity, as evidenced by 5-fold elevations above the upper limit of normal for AST in 3.6% of patients and for ALT in 4.8% of patients and as evidenced by 3-fold elevations above the upper limit of normal for bilirubin in 2.8% of patients. In two patients, drug induced liver injury was documented on liver biopsy. Biochemical evidence of hepatic toxicity was the most common reason for termination of alectinib or for dose modification (dose reduction or suspension in dosing).

- Severe interstitial lung disease (ILD), also observed with other ALK kinase inhibitors, occurred in 0.4% of the 252 alectinib-treated patients.

- Bradycardia (less than 50 beats per minute) occurred in 7.5% of alectinib-treated patients and in 20% of the 221 alectinib-treated patients for whom serial ECGs were obtained. As with other ALK kinase inhibitors, it is expected that alectinib-induced bradycardia may become symptomatic and, in some patients, life-threatening.

- Myalgia or musculoskeletal pain occurred in 29% of the 253 alectinib-treated, with Grade 3 myalgia/musculoskeletal pain occurring in 1.2% and dose modifications required for myalgia/musculoskeletal pain in 0.8% of patients. Among the subgroup of patients (n=218) in whom CPK data were collected, elevation in CPK levels occurred in 43% and Grade 3 elevations occurred in 4.6%,with a median time to Grade 3 CPK elevation of 14 days (interquartile range 13-14 days). Dose modifications for elevation of CPK levels occurred in 5.0% of patients.

Concerns identified through U.S. or foreign postmarketing data
This is the first marketing approval of alectinib in the US; while alectinib is approved outside the US, there was limited post-marketing experience from approval outside the US, with the initial approval in Japan on July 4, 2014.

Potential safety issues that could cause concern when considering how the drug may be used in the postmarket setting.
Safety issues that would raise concern in the post-marketing setting are any adverse reactions which occur with more severe manifestations than those observed in clinical studies (e.g., fatal hepatotoxicity, fatal ILD, rhabdomyolysis) studies as the number of patients exposed to alectinib increases. In addition, based on the observation of permanent visual defects with crizotinib, another drug in this class, the Surveillance and Epidemiology staff were advised to monitor for persistent visual defects. Finally, although the photosensitivity observed with alectinib was mild to moderate in severity with no need for dose modification and patients are

advised to use sunscreens and avoid exposure to sun light, there is the potential for more severe skin reactions, which should be monitored in the post-marketing setting.

9. Advisory Committee Meeting

This NDA was not referred to the Oncologics Drug Advisory Committee because it is not the first drug in its class, the safety profile is acceptable for the proposed indication, the clinical trial design is similar to that used for accelerated approval for patients with NSCLC with no satisfactory alternative therapy, the application did not raise safety or efficacy in the intended patient population, and outside expertise was not necessary as there were no controversial issues that would benefit from advisory committee discussion.

10. Pediatrics

On January 27, 2015, the Office of Orphan Drug Products designed alectinib as an orphan drug for the treatment of ALK-positive non-small cell lung cancer. Therefore, this NDA is exempt from the requirements of the Pediatric Research Equity Act (PREA) for the proposed indication.

11. Other Relevant Regulatory Issues

There are no other outstanding regulatory issues that would preclude approval of this application.

12. Labeling

All review disciplines and labeling consultants (DPPM, OPDP, PLT, and DMEPA) concurred that the agreed-upon final labeling was acceptable.

- *INDICATIONS AND USAGE section:*
  Based on data provided in the NDA, the indication was adequately supported with the exception of the inclusion of patients with locally advanced disease as very limited numbers of such patients were enrolled in clinical trials.

- *DOSAGE AND ADMINISTRATION section:*
  The proposed dosage regimen is adequately supported by the clinical studies as reasonably safe and effective; the recommendation to make up a missed dose was removed, given the half-life of alectinib and its major active metabolite.
- *Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS sections:*
  No contraindications or Boxed Warnings were proposed by Hoffmann-La Roche or by any of the review team members of consultants. The Warnings and Precautions section was revised to include a new subsection on Severe Myalgia and Increased Creatine Phosphokinase (b) (4), based on the requirement for dose modifications in some patients and the potential risk of rhabdomyolysis. The subsection "(b) (4)

[redacted] (b) (4)" was retitled "Hepatotoxicity" to better convey the clinical risk. All sections of the Warnings and Precautions were revised for brevity, removal of exculpatory language [redacted] (b) (4) but retained information characterizing the risks (incidence, time-to-onset, reversibility). The subsection on Photosensitivity was moved from Warnings and Precautions to Adverse Reactions as all but one case was Grade 1 in severity and required no medical intervention or dose adjustments.

- *Patient labeling*
  Patient labeling was proposed by Hoffmann-La Roche and revised by FDA reviewers for consistency with the prescribing information for healthcare providers, consistency with current FDA policies and Guidances on this section of product labeling and risk communication, and for reading level.

- *Carton and container labeling*
  Agreement was reached on final carton and container labeling with Hoffmann-La Roche, DMEPA, and the OPQ reviewers.

13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies (REMS)
  I concur with the recommendations of the DRISK and clinical reviewers that REMS are not required to ensure safe and effective use of alectinib in the indicated patient population. The adverse reactions of alectinib are similar to other products in this class and management of these adverse reactions can be adequately conveyed through product labeling without the need for additional communication or training, based on post-marketing experience with other products in this class.

- Other Postmarketing Requirements and Commitments
  The following post-marketing study is required , under the provisions of 21 CFR 314 Subpart H, to verify the clinical benefit predicted by the durable objective response rates observed with alectinib in patients with ALK mutation-positive NSCLC who are no longer responding to crizotinib:

  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).

  The following post-marketing study is required to determine a reasonably safe dose, if any, of alectinib in patients with moderate to severe hepatic impairment, based on the known metabolism of alectinib and lack of clinical data on pharmacokinetics, safety or efficacy in this population.

  2995-2 Complete a pharmacokinetic trial to determine an appropriate dose of alectinib in patients with moderate to severe hepatic impairment in accordance with the

FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling”.

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

/s/

PATRICIA KEEGAN
12/10/2015