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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	November 25, 2015
From	Gideon M. Blumenthal, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	NDA 208434
Applicant	Hoffman-La Roche Inc.
Date of Submission	July 6, 2015
PDUFA Goal Date	March 4, 2016 (priority)
Proprietary Name / Non-Proprietary Name	Alectinib (ALECENSA)
Dosage form(s) / Strength(s)	150 mg capsules
Applicant Proposed Indication(s)/Population(s)	Treatment of patients with anaplastic lymphoma kinase (ALK) positive locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib
Recommendation on Regulatory Action	*Accelerated Approval*
Recommended Indication(s)/Population(s)	Treatment of patients with anaplastic lymphoma kinase (ALK) positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib

Discipline and Consultants	**Primary/ Secondary Reviewer**
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CMC Reviews	Drug Substance: Charles Jewell, Ph.D. Drug Product/ Environmental Assessor: Rajiv Agarwal, Ph.D. Process/Microbiology: Zhaoyang Meng, Ph.D. Facility: Zhong Li, Ph.D. Biopharmaceuticals: Gerlie Gieser, Ph.D. RBPM: Steven Kinsley Application Technical Lead: Olen Stephens, Ph.D. ORA Lead: Paul Perdue, Jr.
Clinical Pharmacology Reviews	Clin Pharm: Stacy Shord, Pharm.D./ Hong Zhao, Ph.D. Pharmacometrics: Jingyu Yu, Ph.D./Yaning Wang, Ph.D. PBPK: Ping Zhao, Ph.D./ Vikram Sinha, Ph.D. QT-IRT: Dinko Rekic, Ph.D., Jiang Liu, Huifang Chen, Qianyu Dang, Ph.D., Michael Y Li, Norman Stockbridge, M.D
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1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Alectinib is a kinase inhibitor that inhibits Anaplastic Kinase Inhibitor (ALK). ALK fusions are present in about 3-7% of non-small cell lung cancer patients. Non-clinical studies indicate that alectinib has activity against intrinsic and acquired mechanisms of ALK inhibitor resistance, including against gatekeeper point mutations in the ALK kinase domain, and in the Central Nervous System (CNS) compartment. ALK-positive metastatic non-small cell lung cancer (mNSCLC) after progression on crizotinib (a first-generation ALK inhibitor) is a serious and life threatening condition, with median survival of less than two years and frequent CNS metastasis. There is an unmet medical need for patients with ALK-positive mNSCLC who progress on crizotinib, with no available therapies specifically for this patient population. Current options after progression on crizotinib include the ALK inhibitor ceritinib, which currently has accelerated approval and is associated with an overall response rate (ORR) of approximately 44% and a median duration of response (DOR) of approximately 7 months. The response to single agent chemotherapy or platinum-doublet chemotherapy after progression on crizotinib in this patient population is not precisely known, but is likely relatively low and associated with substantial toxicity.

In the two single arm, open label studies of alectinib 600 mg bid in patients with ALK+ mNSCLC who progressed on crizotinib, the confirmed ORR by central radiologic review is 38% (95% CI: 28, 49) and 44% (95% CI: 36, 53) with median DOR of 7.5 months and 11.2 months. The pooled CNS ORR in patients with measurable CNS lesions was 61% (95% CI: 46, 74) with a median CNS DOR of 9.1 months. The safety of alectinib was acceptable relative to the benefits. Common adverse reactions include fatigue, constipation, edema, and myalgia. Common laboratory abnormalities include increased transaminases, increased alkaline phosphatase, increased CPK, and increased bilirubin. Rare but serious adverse reactions include drug induced liver injury, interstitial lung disease, and severe myalgia and CPK elevation. Risk will be managed by product labeling and two post-marketing requirement (PMR) studies. The Accelerated Approval PMR will be to confirm clinical benefit by submitting the results of the ongoing BO28984 (ALEX) study: a randomized, phase 3 study comparing alectinib with crizotinib in treatment-naïve ALK positive mNSCLC. The 505o PMR will be to submit the results of a study of alectinib in patients with severe hepatic impairment.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Approximately 2-7% of mNSCLC tumors harbor ALK rearrangements • Survival for patients with ALK-positive mNSCLC who progress on crizotinib is poor, with median survival likely less than 2 years • CNS metastasis is a frequent site of progression	ALK-positive metastatic NSCLC after progression on crizotinib is a serious life-threatening condition with poor prognosis. CNS metastasis is a frequent occurrence.
Current Treatment Options	• There is currently no available therapy indicated for the treatment of patients with ALK-positive mNSCLC who progressed on crizotinib. • Ceritinib is an ALK kinase inhibitor that currently has accelerated approval for the treatment of ALK-positive mNSCLC patients who progress on crizotinib. Ceritinib is associated with an ORR of 44% and a median DOR of 7.4 months. • Other treatment options for ALK+ mNSCLC progressing on crizotinib include chemotherapy, either as a single agent (docetaxel or pemetrexed) or as a platinum-based doublet. The ORR and DOR of single agent or doublet chemotherapy in this specific patient population is not known. In mNSCLC patients who are ALK inhibitor naïve, the ORR to platinum doublet chemotherapy is 45%, and to single agent chemotherapy is 20%. Chemotherapy is associated with toxicity, including fatigue, myelosuppression, and neuropathy.	There is an unmet medical need for patients with ALK-positive metastatic NSCLC who experience disease progression on crizotinib, with no available therapies specifically for this patient population.
Benefit	• The pivotal trials supporting efficacy in this NDA, Studies NP28761 (N=87) and NP28673 (N=138), are two single arm trials assessing alectinib 600 mg BID in patients with ALK-positive mNSCLC who have progressed on crizotinib. • The observed objective response rates of 38% and 44% in these studies are clinically meaningful for patients with ALK-positive NSCLC who have progressed following therapy with crizotinib. • The median DOR of 7.5 months and 11.9 months indicates that responses are relatively durable. • A pooled analysis in patients with measurable CNS lesions at baseline (n=51) demonstrated a CNS ORR of 61% and CNS median DOR of 9.1 months. • A limitation of single arm trials is the potential for known and	The submitted evidence meets the statutory evidentiary standard for accelerated approval. The observed ORRs are clinically meaningful when considering the intended patient population. The duration of response results and CNS ORR and DOR are supportive. Based on the demographic and baseline disease characteristics for the patients enrolled, the overall population in these studies is comparable to the overall U.S. target population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	unknown patient selection bias.	
Risk	• The safety database for this NDA review includes a total of 253 patients exposed to alectinib at a dose of 600 mg BID across Studies NP28761 and NP28673. • Permanent discontinuation of alectinib due to adverse reactions occurred in 5% of patients. Twenty seven percent of patients had alectinib dosing interrupted for adverse reaction. • The most common adverse reactions were fatigue (41%), constipation (34%), edema (30%), and myalgia (29%). • Safety issues considered significant and serious enough to warrant inclusion in the Warnings and Precautions section of the USPI for alectinib are: hepatotoxicity, interstitial lung disease, bradycardia, and severe myalgia and creatine phosphokinase (CPK) elevation. • Off-label use in patients other advanced cancers with ALK or RET rearrangement is anticipated, but there are no specific safety concerns related to this potential off-label use in these patients with life-threatening disease. • A limitation of single arm trials is the lack of controlled safety data.	Alectinib appears to have a reasonable safety profile when assessed in the context of the treatment of a life-threatening disease. The rate of permanent discontinuation of alectinib due to adverse reactions was low. Additional safety information is expected in the future from the ongoing randomized, controlled trial of alectinib versus crizotinib in the treatment of treatment-naïve patients with ALK-positive advanced NSCLC.
Risk Management	• The safety concerns of hepatotoxicity, interstitial lung disease, bradycardia, and severe myalgia and creatine phosphokinase (CPK) elevation identified in the summary assessment of risk can be adequately addressed through product labeling. • An accelerated approval PMR is recommended to confirm clinical benefit by establishing the superiority of alectinib over available therapy in patients with metastatic ALK-positive NSCLC. • A 505o PMR is recommended to determine an appropriate dose of alectinib in patients with moderate to severe hepatic impairment. • There were no significant safety concerns identified during NDA review requiring risk management beyond labeling or warranting consideration for Risk Evaluation and Mitigation Strategy (REMS).	Risk management through product labeling and pharmacovigilance. The Accelerated Approval PMR to submit the results of the ongoing BO28984 (ALEX) randomized controlled trial of alectinib versus crizotinib in ALK-inhibitor naïve mNSCLC to confirm clinical benefit and the 505o PMR for patients with severe hepatic impairment will address uncertainties currently present at the time of accelerated approval.

2. Background

Product Information:
On July 6, 2015, Hoffman-La Roche Inc. (heretofore referred to as the Applicant) submitted the NDA 208434 for alectinib (Alecensa; CH5424802; RO5424802) for a proposed indication of treatment of patients with anaplastic lymphoma kinase (ALK) positive locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

Alectinib is a new molecular entity (NME) tyrosine kinase inhibitor of ALK. Alectinib and the active M4 metabolite demonstrated in vitro and in vivo activity against multiple mutant forms of the ALK enzyme, including some mutations identified in NSCLC tumors in patients who have progressed on crizotinib. In mouse models implanted with tumors carrying ALK fusions, administration of alectinib resulted in antitumor activity and prolonged survival, including in mouse models implanted intracranially with ALK-driven tumor cell lines. Thus, a goal of the alectinib development program was to overcome intrinsic and acquired mechanisms of crizotinib resistance, including penetration into CNS sanctuary sites. Alectinib is being studied under IND 111,723 which was activated on October 28, 2011. Based on preliminary clinical evidence of a substantial improvement over available therapy, FDA granted alectinib Breakthrough Therapy Designation on June 26, 2013.

The primary efficacy data for this NDA is the results from 225 patients enrolled in study NP28761 or NP28673, two, multi-center, open-label, single arm studies of patients with metastatic ALK positive NSCLC who progressed on crizotinib treated with alectinib 600 mg twice daily.

Lung cancer is the leading cause of cancer death in the U.S., with more people dying of lung cancer than of colon, breast, and prostate cancers combined. It is estimated that there will be 158,040 deaths due to lung cancer in 2015, comprising 27% of all cancer deaths in the U.S. NSCLC accounts for approximately 85% of lung cancer, with an expected 5-year survival of 1-5% for advanced disease.

Approximately 3 to 7% of patients with NSCLC harbor ALK fusions (Soda et al., Nature 2007). ALK fusions are more common in light smokers (e.g. < 10 pack years) or never smokers, younger patients, and patients with adenocarcinoma and acinar or signet-ring features (Kwak et al. NEJM 2010).

Several ALK rearrangements have been described in NSCLC. The majority are comprised of parts of the echinoderm microtubule-associated protein-like 4 (EML4) gene with the ALK gene. In NSCLC, at least nine different EML4-ALK fusion variants have been identified. In addition, non-EML4 fusion partners have been identified, including KIF5B-ALK and TFG-ALK.

Therapeutic context

FDA approved therapies specifically for ALK-positive metastatic NSCLC include crizotinib and ceritinib. Crizotinib initially received accelerated approval based on Overall Response Rate (ORR) and Duration of Response (DOR) of large magnitude in single arm trials in 2011. Subsequently, crizotinib received traditional approval based on improvements in Progression-free survival, ORR and DOR compared to chemotherapy in two randomized controlled trials (Shaw AT et al NEJM 2013; Solomon BJ et al NEJM 2014).

Ceritinib received accelerated approval (and thus is not considered an available therapy) for patients with ALK-positive metastatic NSCLC who progressed on crizotinib in 2014 based on an ORR of 44% (95% CI; 36, 52) by independent review committee in 163 patients, with a 7.1 month median DOR. Ceritinib is associated with frequent adverse reactions, including GI toxicity (96% all grades; 14% severe). Dose reduction for ceritinib-related toxicity is common, occurring in over half of patients.

Unfortunately, resistance invariably occurs to crizotinib, frequently in the CNS. To date, several different point mutations with the ALK tyrosine kinase domain have been found in patients with acquired resistance to crizotinib. New therapies are needed for patients with ALK positive mNSCLC who progress on crizotinib.

Regulatory background and marketing history:

On July 4, 2014, Alectinib was approved in Japan for the treatment of unresectable advanced/relapsed ALK fusion gene-positive NSCLC.

The following summarizes the key milestones in the U.S. regulatory history:

- **July 18, 2011**: Pre-IND meeting with Chugai Pharmaceutical Co, Ltd and FDA to discuss ongoing phase 1/2 study in Japan (AF-001JP) and planned phase 1/2 IND-enabling study. FDA noted (b) (4) for the purposes of accelerated approval.
- **October 28, 2011**: IND- enabling study (AF-002JG A Phase 1/2 study of CH5424802 in Patients with ALK-rearranged NSCLC) allowed to proceed under IND 111,723.
- **December 21, 2012**: Change of IND sponsor from Chugai Pharma USA, LLC to Hoffman-La Roche, Inc.
- **June 26, 2013**: Breakthrough Therapy Designation Request Granted. Primary basis was an early analysis of the phase 1/2 study in the US (AF-002JG/NP28761) showing ORR of 48% in 21 evaluable ALK+ NSCLC patients who progressed on crizotinib. Also supportive data from the phase 1/2 study (AF-001JP) in Japan of 70 ALK+ NSCLC patients who were crizotinib-naïve showing an ORR of 94% (95% CI: 82, 99)
- **July 22, 2013**: Type B Post-Breakthrough Designation meeting. FDA agreed that results from Studies NP28761/AF-002JG and NP28673, with 250 patients treated at the RP2D dose to be marketed in the United States, can potentially permit a

substantive review for accelerated approval. FDA generally agreed that verification of clinical benefit would be obtained in the randomized, active-controlled trial, BO28984. FDA noted that the toxicological assessment provided for (b) (4) sodium lauryl sulfate (SLS) in the formulation of the drug product to be marketed (b) (4) Roche 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 recommended (b) (4) Roche plans to conduct a clinical-PK (relative BA) trial using alternate formulations (b) (4) FDA agreed to continue discussions on the acceptability on the proposed formulation for commercial marketing.

- **October 23, 2013**: Type B CMC Post- Breakthrough Discussion. FDA stated that Hoffman-La Roche has not justified the proposed level of SLS based on toxicological data. At this time there is inadequate safety experience in clinical trial subjects using the proposed formulation and dose of RO5424802 which Hoffmann-La Roche intends to market in the US. It may be possible to support the safety of the proposed formulation and dose of RO5424802 in the planned risk-benefit analysis derived from 250 patients at the recommended phase 2 dose currently being studied in clinical trials. The proposed study design appears reasonable to compare the exposure of the different formulations at a dose of 600 mg. However, previously provided dissolution data indicate (b) (4) Therefore, the proposed RBA study should include an additional arm for the (b) (4) % formulation.
- **September 30, 2014**: Type C pre-NDA meeting content and format.
- **November 17, 2014**: Type B meeting to discuss plans to characterize the drug metabolism and PK of alectinib's metabolites, the results of studies regarding

toxicology evaluation of SLS formulation and the clinical pharmacology program to support the NDA. Based on the data provided in the meeting package, FDA agreed that administration of RO5424802 containing (b) (4)% SLS did not appear to lead to increased toxicity in male rats compared to the formulation without SLS. FDA also noted that SLS did not appear to affect the exposure level of RO5424802 in this study. The study, therefore, does help to alleviate immediate nonclinical toxicology concerns regarding the safety of the SLS content of the clinical formulation that will be used for registration; however, given the previously documented toxicological assessment of SLS, and as mentioned in previous meeting minutes, FDA continues to encourage Roche to study alternate formulations of alectinib (b) (4)

- **March 19, 2015**: Type B CMC Meeting
- **April 7, 2015**: Type B preNDA Meeting: FDA agreed 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).

3. Product Quality

General product quality considerations: Alectinib HCl is a white to yellow white powder or powder with lumps. The IUPAC name for Alectinib is 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 equating to a molecular weight of 519.08 g/mol. The molecule is achiral and has a molecular formula of C30H35ClN4O2. The drug substance has low solubility in aqueous buffers across the entire pH range. In acidic conditions, the low solubility is attributed to the common-ion effect with HCl buffers. Alectinib is slightly hygroscopic. (b) (4) have been observed for Alectinib HCl. was selected for development. Alectinib HCl is stored in (b) (4) not above 30 °C protected from light.

The proposed commercial formulation is an immediate-release capsule formulation with standard excipients manufactured using conventional equipment and manufacturing processes (b) (4) A single 150 mg strength is proposed for commercialization.

Alectinib hard capsules, 150 mg are white, Size 1 capsules with "ALE" printed in black ink on the cap and "150 mg" printed in black ink on the body. The capsule drug product are packaged in a round, white, 250 mL high-density polyethylene bottle with a child-resistant, (b) (4) screw cap and an integrated desiccant. The capsules are formulated with alectinib HCl, lactose monohydrate, hydroxypropylcellulose, sodium laury sulfate, carboxymethyl cellulose calcium, magnesium stearate, (b) (4) into a capsule shell composed of carrageenan, potassium chloride, titanium dioxide,

carnauba wax, corn starch, hypromellose, and printing ink (red iron oxide, yellow iron oxide, FD&C Blue No. 2 aluminum lake, carnauba wax, white shellac, glyceryl monooleate, [redacted]).

A 150 mg hard capsule formulation containing [redacted] Sodium lauryl Sulfate (SLS) was developed in [redacted]. This formulation was used in the Phase 1/2 studies NP28673 (global) and NP28761 (US and Canada), and the global Phase 3 study BO28984.

[redacted] SLS is [redacted]% of the drug strength, but [redacted]% of the total capsule weight. The amount of SLS [redacted] capsule) is [redacted] approved by the FDA. Since the dose is 1200 mg/day, this will account for [redacted] of SLS intake each day. Given the favorable toxicity profile of alectinib, this amount of SLS appears acceptable given the patient population.

The manufacturing process follows a [redacted]

Based on 12 months of stability data for the three stability batches and stability data for three supportive batches, 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 °C and protected from light.

BCS Classification is 4. Drug substance has low solubility (in aqueous buffers across the physiologic pH range) and low permeability (absolute bioavailability is 37%). Drug product is [redacted]).

- *Facilities review/inspection:* Final recommendations for manufacturing site Chugai Pharmaceutical Co, Ltd (DP Registration Stability Testing) is pending at the time of finalization of this CDTL review.

- *Other notable issues (resolved or outstanding)*: None.

- **Final Recommendation (Olen Stephens, Ph.D.) 11/5/15:** OPQ recommendation is for approval pending "acceptable" recommendation from the facilities reviewer regarding the manufacturing and facilities status.

4. Nonclinical Pharmacology/Toxicology

- *General nonclinical pharmacology/toxicology considerations*: the established pharmacologic class of alectinib is kinase inhibitor. In biochemical screening assays, alectinib inhibited ALK and RET kinase as well as multiple point mutations of both kinases at concentrations of less than 30 nM. In cellular assays, incubation with alectinib resulted in inhibition of ALK phosphorylation and downstream signaling

proteins STAT3 and AKT. In mice subcutaneously implanted with ALK-driven lung, neuroblastoma, or lymphoma cell lines, alectinib inhibited in vivo tumor growth. Administration of alectinib to mice intracranially implanted with an EML4-ALK driven lung cancer tumor cell line resulted in improved survival compared to treatment with vehicle control or crizotinib, supporting the ability of alectinib to penetrate the blood brain barrier.

The major target organs in general toxicology studies conducted in rats and monkeys included the GI tract, adrenal gland, liver, and lungs, with minimal to mild severity. In the GI tract and lungs, there were findings consistent with hemorrhage, correlating with increases in APTT and PT at the highest dose levels in rats. Findings in rats of decreased trabecular bone and increased osteoclast activity along with dental findings are potentially relevant to a pediatric population and are included in section 8.4 of the label. To support the use of the clinical formulation of alectinib intended for initial marketing which includes (b) (4) SLS ((b) (4)% w/w), the Applicant conducted a nonclinical study in rats at a single dose level comparing the clinical and nonclinical formulations. (b) (4) SLS did not significantly affect toxicity, including GI toxicity, or PK of alectinib in this study, supporting the safety of the initial clinical formulation.

In safety pharmacology studies, alectinib did not cause significant changes in CNS, respiratory, or GI motor function. Alectinib did demonstrate some potential for QT prolongation in the in vitro hERG assay (IC50=0.12 uM), though QT prolongation was not observed in in vivo cardiovascular studies and has not been reported clinically. At doses > 20 mg/kg single dose administration of alectinib resulted in modest decreases of blood pressure. In the repeat dose toxicology study, monkeys treated at the high dose level displayed decreases in heart rate, consistent with bradycardia observed clinically.

- *Carcinogenicity*- studies were not conducted to support approval of alectinib in patients with advanced cancer, in accordance with ICH S9. Alectinib was not mutagenic in the bacterial reverse mutation assay or clastogenic in the in vitro Chinese Hamster Lung assay, but was positive in the in vivo micronucleus assay. The results of a second in vivo micronucleus test were supportive of an increase in numerical rather than structural aberrations. Because of this finding, men with female partners of reproductive potential are advised to use contraception during and for 3 months following the final dose of alectinib.

- *Reproductive toxicology*- distribution studies in pregnant rats suggest that alectinib is able to cross the placenta. In embryofetal studies in rats and rabbits, alectinib was embryotoxic at maternally toxic doses. In rats treated at 9 mg/kg/day (approximately 2.7 times the exposure at the recommended human dose) maternal weight loss and developmental toxicities occurred. At 27 mg/kg/day there was complete litter loss. In the rabbit embryofetal studies, at approximately 3 times the recommended human dose, abortion or complete embryofetal mortality occurred in three of six rabbit litters. The remaining three litters had few live fetuses, decreased fetal and placental weights, and

other defects. A warning for the risk of embryofetal toxicity is recommended. In addition, specific recommendations for contraception in females are recommended.

- **Final Pharm Tox Recommendations (Drs. Zahalka, Ringgold, Helms) 11/6/2015**: There are no nonclinical findings that would preclude approval of alectinib for the proposed indication.

5. Clinical Pharmacology

The clinical pharmacology program is comprised of eight clinical studies. There were 5 studies in healthy subjects: NP29040- relative bioavailability (BA) and bioequivalence with capsules with different SLS concentrations (n=97); NP28989- absolute BA and mass balance (n=6); NP28990- drug interaction with posaconazole (N=23); NP29042- drug interaction with rifampicin (N=24); and NP28991- food and drug interaction with esomeprazole (N=42). In addition, there were 3 studies in patients with cancer: NP28761- dose escalation from 240 mg bid to 900 mg bid (N=47); NP28673- dose escalation 600 mg bid (N=6); NP28673- drug interaction with midazolam (N=15).

- *Absorption*- absolute BA of alectinib 600 mg within 30 minutes of a meal was 37% in healthy volunteers. Median Tmax in cancer patients was about 4 hours.
- *Distribution*- the population apparent central volume of distribution (V/F) was 4,016L for alectinib and 10,093L for M4 based on the pop PK model. Alectinib and M4 are highly plasma protein bound and predominantly distributed to blood cells. Alectinib demonstrated penetration into the CNS in the 8 patients with CNS metastases who consented to optional lumbar puncture in study NP28761. Alectinib concentrations in the cerebrospinal fluid (CSF) were 0.2% to 0.5% of concentrations in plasma. CSF concentrations correlated with plasma concentrations.
- *Metabolism*- primarily metabolized by CYP3A4 to the major active metabolite M4, accounting for about 40% of metabolism based on the pop PK model. M4 is subsequently metabolized by CYP3A4.
- *Elimination*- mass balance suggests that alectinib is primarily eliminated in the feces; biliary excretion and metabolism contribute to elimination of alectinib.
- *Excretion*- estimated population geometric mean (CV, %) CL/F was 1,965 L/H (82%) for alectinib and was 5,205 L/h (217%) for M4. The geometric mean elimination half-life was 32 hours (36%) for alectinib and 31 hours (46%) for M4 in cancer patients based on the pop PK model
- *PK parameters*- alectinib demonstrated linear exposure over a range of 460 mg to 900 mg after a single dose or at steady state under fed conditions. Accumulation of alectinib and M4 at steady-state is about 6-fold. Steady state concentrations were reached by day 7 in the pop PK model. For alectinib, the estimated between-patient variability in CL/F and in V/F was 40% each. For M4, the estimated between-patient variability in CL/F was 36% and in V/F was 59%. Body weight was the only covariate to significantly but modestly affect CL/F and V/F. Other covariates such as age, BMI, BSA, CNS metastases, mild hepatic

impairment, mild to moderate renal impairment, performance status, ethnicity, gender, prior chemotherapy status, race, smoking status, and tumor size did not impact alectinib or M4 PK.

- *Renal impairment*- no clinically meaningful effect on alectinib or M4 exposure.
- *Hepatic impairment*- no dose adjustment for patients with mild hepatic impairment. A PMR will be issued to study patients with moderate to severe hepatic impairment.
- *Drug-Drug interactions*- Alectinib and M4 are CYP3A4 substrates. Alectinib and M4 inhibited CYP3A4 and induced CYP3A4 and CYP2N6 in vitro, and alectinib inhibited CYP2C8 in vitro. They both inhibited MDR1 and BCRP in vitro. Rifampin (CYP3A4 inducer) decreased alectinib exposure 73% and increased M4 by 1.8 fold, but no clinically meaningful changes to combined exposure were observed. Therefore, no dose modification for co-administration of alectinib with CYP3A inducer is necessary. Posaconazole (CYP3A4 inhibitor) increased alectinib exposure 1.8 fold and decreased M4 by 25%. The combined exposure increased 1.4 fold. No dose modification is recommended for co-administration with a CY3A inhibitor. A midazolam sub-study demonstrated that alectinib or M4 is unlikely to induce CYP3A in humans.
- *Acid Reducing Agents (ARA)*- Alectinib is a weak base that demonstrates low solubility and pH dependent solubility. No clinically meaningful effect on individual exposures or combined exposures (alectinib and M4) when esomeprazole was co-administered. No dose or schedule modification is recommended for patients taking alectinib with ARAs.
- *Food Effect*- individual and combined exposure of alectinib and M4 were about 3-fold higher when taken with a high-fat meal compared to a fasted state. It is recommended that alectinib be taken in the fed state as food increases alectinib exposure and was administered with food in the registration trials.
- *Exposure response (E-R)*- The Applicant stated that change in tumor size from baseline, across the range of 300 mg bid to 900 mg bid, show that higher median steady state trough concentrations are associated with a greater reduction in tumor size. Furthermore, a plateau appears to be reached at the observed median steady state trough level corresponding to a dose of 600 mg BID. The Applicant states that a significant reduction in tumor size over time was observed in all exposure categories (i.e. low, medium and high) for patients treated at a dose of 600 mg BID. FDA pharmacometrics concluded that there was no E-R relationship observed between best overall response and the combined average concentration of alectinib and M4. Furthermore, they concluded that there was no E-R relationship for best overall response in the CNS and the combined average concentration. Finally, they concluded that there was no E-R relationship for grade 3 or higher AEs or SAEs and the combined average concentration.
- *Dose selection*- was based on safety and activity observed in dose finding portion of NP28761 (n=46) evaluating doses of 240 mg to 900 mg bid in the fed state. Two dose limiting toxicities were observed in the dose escalation portion following a dose of 900 mg BID administered with food (grade 3 headache and grade 3 neutropenia). These events occurred before day 10 and lasted 5 to 9 days.

Based on these observations, the Applicant identified a dose of 600 mg BID as the recommended phase 2 dose.

- *QTc assessment*- no large mean change (i.e. >20 msec) in QTc interval and no concentration-QTcF relationship was observed in patients administered a dose of 600 mg BID with food (pooled data using 217 patients from NP28761 and NP28673). Two patients experienced QTcF > 500 msec or > 60 msec. No cases of Torsades or deaths associated with QT prolongation were reported in the safety database.

- **Final Recommendation (Drs. Shord, Yu, Wang, Zhao, Sinha, Zhao, Rahman) 11/6/2015:** This NDA is acceptable for approval from a clinical pharmacology perspective.

6. Clinical Microbiology

Not Applicable.

7. Clinical/Statistical- Efficacy

I agree with the conclusions of the clinical efficacy (Dr Larkins.) and statistical (Dr. Chen) reviewer assessments.

Efficacy Summary:

Study NP28761: a multi-center, open-label, single arm study taking place at North American sites in patients with locally advanced or metastatic ALK-positive NSCLC. The phase I portion was designed to consist of two cohorts, a fasting cohort and a non-fasting cohort, with a planned enrollment of 12 patients. In the phase II portion of NP28761, patients were to be administered alectinib at the recommended dose and administration conditions. As initially designed, planned enrollment for the phase II portion of NP28761 was 54 patients, with simultaneous enrollment of two sub-populations of patients: Sub-population A, consisting of patients who had progressed on crizotinib (n=49), and Sub-population B, consisting of patients who had never received an ALK inhibitor (n=15).

In the Phase 1 portion, a total of 58 patients were screened for entry. There were 10 screen failures. A total of 48 patients were enrolled, and 47 patients received at least one dose of alectinib; one patient did not receive alectinib, due to symptomatic brain metastasis.

In the Phase 2 portion, a total of 125 patients were screened for entry. There were 38 screen failures. A total of 87 patients were enrolled, all of whom received at least one dose of alectinib 600 mg. The median duration of follow-up was approximately 4.8 months (range 1.1 to 13.7 months).

In the phase 1 portion (n=47), the investigator-assessed ORR was 59.6% (95% CI 44.3, 73.6) across all dose cohorts. The median duration of response was 11.0 months. Based on

safety, tolerability, pharmacokinetic, and efficacy data, alectinib 600 mg BID was chosen as the RP2D for the phase 2 portion of Study NP28761.

In the phase 2 portion (n=87), baseline disease demographic and disease characteristics were: median age 54 years (range 29 to 79), 84% White and 8% Asian, 55% female, 90% ECOG performance status 0 or 1, 100% never or former smokers, 99% stage IV, 94% had adenocarcinoma histology, and 74% had prior chemotherapy. Efficacy results based on IRC assessments in the Response Evaluable (RE) population were proposed by the Applicant for inclusion in the USPI. However, the review division contended that efficacy results based on analysis of the ITT population is more appropriate for inclusion in the USPI. ORR by IRC for both the RE and ITT populations are presented in table 1. Median duration of response was 7.5 months.

Table 1: Primary Endpoint Efficacy Results for Study NP28761

	RE (n=69)	ITT (n=87)
ORR	48%	39%
(95% CI)	(36, 60)	(28, 49)

Study NP28673

A global, multi-center, open-label, single arm study designed to be conducted in three parts – a phase 1 portion, a phase 2 portion, and a post-progression treatment portion - in patients with locally advanced or metastatic ALK-positive NSCLC with progression on crizotinib.

Part 1 was designed as a 3+3 dose-escalation to assess the safety, tolerability, and pharmacokinetics of alectinib at dose levels or 600 mg twice daily and 900 mg twice daily with a planned enrollment of up to 12 patients (actual enrollment was 6 patients treated at 600 mg bid and rolled into Part 2).

In Part 2 of NP28673, patients were to be administered alectinib at the RP2D on a 28 day cycle. Planned total enrollment to the study was 130 patients, consisting of two groups of patients: those who have received at least one line of platinum-based cytotoxic chemotherapy for NSCLC (minimum of 85 patients) and those who are naïve to any cytotoxic chemotherapy treatments for NSCLC (maximum of 45 patients). Part 3 of the study offered patients continued treatment on study following progression of disease.

For Part 2 of the study, the co-primary endpoints were ORR based on IRC review using RECIST 1.1 criteria in the overall population (with and without exposure to chemotherapy) and in the population with prior exposure to chemotherapy. Confirmed responses are those that persist on repeat imaging study ≥4 weeks after initial documentation of response.

The original null hypothesis (H_0) was a best ORR of 50%, with an assumed alternative hypothesis of a best ORR of 65%. For Part 2 of the study, with two-sided alpha of 0.05, this design provided 80% power to reject the null hypothesis with 85 patients. The protocol used a Simon two-stage design for Part 2 of the study, with plans for a non-binding interim futility analysis to be performed when at least 30 patients have a response assessment. If

the futility analysis results showed ORR <30%, then the study might be terminated for futility; otherwise, enrollment would continue until approximately 130 patients in total were enrolled to the study. Hierarchical testing was planned for the co-primary endpoints, with ORR in the all-patients group (patients with and without prior chemotherapy) the first endpoint tested. If this result was positive, then the same null hypothesis would be tested with two-sided alpha of 0.05 in the group of patients with prior exposure to chemotherapy.

The primary analysis set for efficacy endpoints was modified in Version 4 of the protocol, dated 19 Nov 2013. According to Version 4, the Response Evaluable (RE) population would be used to analyze the primary endpoint of ORR. The RE population was defined as patients with measurable disease at baseline who have a baseline tumor assessment and received at least one dose of alectinib.

The efficacy results for Study NP28673 are based on a data cut-off date of 18 Aug 2014, except for updated analyses for selected IRC-assessed efficacy endpoints, which are based on a data cut-off date of 8 Jan 2015. Submission of these updated efficacy analyses for review was agreed upon between the Applicant and the FDA.

A total of 176 patients were screened for entry into the phase 2 portion of the study. There were 37 screen failures. A total of 139 patients were enrolled, 138 of whom received at least one dose of alectinib 600 mg; one enrolled patient did not receive study drug due to withdrawal on C1D1 for out of range laboratory values. The median duration of follow-up was approximately 7.0 months (range 0.6 to 12.2 months).

The primary efficacy results for Study NP28673 are based on updated analyses for IRC-assessed efficacy endpoints, using a data cut-off date of 8 Jan 2015. The results of investigator-assessed efficacy endpoints are based on the initial data cut-off date of 18 Aug 2014.

A summary of ORR by RE and ITT in all patients and chemotherapy treated patients is presented in Table 2. All responses were partial responses. Median duration of response was 11.2 months for the ITT All patient population.

Table 2: Primary Endpoint Efficacy Results for Study NP28673

	All Patients		**Patients with Prior Chemotherapy**	
	RE (n=122)	**ITT (n=138)**	**RE (n=96)**	**ITT (n=110)**
ORR (95% CI)	50% (41, 53)	44% (36, 53)	44% (34, 54)	39% (30, 49)

Table 3 shows a pooled analysis of CNS Objective Response rate and CNS Duration of response in patients with measurable CNS lesions in studies NP28761 and NP28673.

Table 3: Pooled Analysis of CNS Objective Response Rate in Patients with Measurable CNS Lesions in NP28761 and NP28673

Efficacy Parameter	**N=51**
CNS Objective Response Rate (95% CI)	61% (46, 74)
Complete Response	18%
Partial Response	43%
CNS Duration of Response, median in months (95% CI)	9.1 (5.8, not evaluable)

Primary Reviewer Conclusions:
I concur with Dr Larkins that the magnitude of ORR and DOR from studies NP28761 and NP28673 is reasonably likely to predict clinical benefit over available therapies in the proposed patient population. Furthermore, the ORR and durability in the CNS with alectinib is clinically meaningful for patients.

Conclusions on the Substantial Evidence of Effectiveness: The Applicant has provided substantial evidence of effectiveness required to support accelerated approval. The application contains such evidence and alectinib has been shown to be effective on surrogate endpoints (ORR and DOR) reasonably likely to predict clinical benefit for its intended use, patients with metastatic ALK+ NSCLC who progressed on crizotinib. Of note, ORR of large magnitude is likely associated with a large magnitude of PFS effect in metastatic NSCLC (Blumenthal et al, JCO 2015). Effects on ORR and DOR appeared to be consistent across study NP28761 and NP28673, and were supported by CNS ORR and DOR.

8. Safety

I concur with the safety analysis conducted by Dr Larkins. The safety assessment of alectinib was pooled across two single arm, open-label trials, NP28761 and NP28673 evaluating 253 patients with ALK-positive NSCLC treated with alectinib 600 mg twice daily. The median duration of exposure was 9.4 months. Seventy percent of patients were exposed for at least 6 months and 40% for at least 1 year. The population characteristics were: median age 53 years, age less than 65 (86%), female (55%), White (74%), Asian (18%), adenocarcinoma (96%), never or former smoker (98%), performance status 0 or 1 (91%), prior chemotherapy (78%).

- *Adequacy of the drug exposure experience*: the median exposure of 9.4 months in 253 patients is adequate for accelerated approval, given the benefits. Please note that lower frequency events (e.g. <2%) may be unmasked with broader patient experience and exposure to alectinib.

- *Adequacy of the clinical safety assessments, including data integrity and submission quality, categorization of adverse events and clinical assessments*: no concerns
- *Key safety results*:
    - Deaths: occurred in 2.8% of patients, including hemorrhage (0.8%), intestinal perforation, (0.4%), dyspnea (0.4%), pulmonary embolism (0.4%), and endocarditis (0.4%).
    - Serious adverse events (SAEs): occurred in 19% of patients, most commonly pulmonary embolism, dyspnea and hyperbilirubinemia (1.2% each).
    - Discontinuations due to AEs: occurred in 6% of patients, most frequently due to hyperbilirubinemia and increased ALT (1.6% each).
    - Dose reductions were necessary in 23% of patients, most frequently due to elevations in bilirubin (6%) or CPK (4.3%).
    - The most frequent AEs (>25%) were fatigue, constipation, edema, and myalgia.
    - The most frequent grade 3-4 AEs (>1%) were dyspnea, fatigue, myalgia, headache, and diarrhea.
    - The most frequent laboratory abnormalities (>40%) were increased ALT, increased alkaline phosphatase, increased CPK, and Anemia.
    - The most frequent grade 3-4 laboratory abnormalities (>4%) were increased CPK, increased ALT, hypokalemia, and lymphopenia.
- *Evaluations of submission-specific safety issues*:
    - Hepatotoxicity: Two patients with grade 3-4 AST/ALT elevations had documented drug induced liver injury by liver biopsy.
    - Interstitial Lung Disease (ILD)/ pneumonitis: grade 3 occurred in one patient (0.4%).
    - Bradycardia: occurred in 7.5% of patients treated with alectinib and appears to be a consistent effect across ALK kinase inhibitors.
    - Severe myalgia and Creatine Phosphokinase (CPK) elevation: Myalgia or musculoskeletal pain occurred in 29% of patients (1.2% grade 3). Elevations in CPK occurred in 43% of patients (4.6% grade 3).
- *Concerns identified through foreign post-market experience*: No concerns identified from the Japanese post-market experience to date.
- *Potential safety issues that could cause concern when considering how the drug may be used in the post-market setting*: Pharmacovigilance may be necessary to track cases of rhabdomyolysis and visual loss, given the mechanism of action of the drug.

Primary Reviewer Conclusions: I concur with Dr. Larkins that the risks of alectinib are acceptable relative to the benefits and can be managed through product labeling and pharmacovigilance.

9. Advisory Committee Meeting

There was no advisory committee meeting for alectinib because the safety profile is acceptable for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on crizotinib, the application did not raise significant public health questions on

the role of alectinib for this indication, and outside expertise was not necessary since there were no controversial issues that would benefit from an advisory committee discussion.

10. Pediatrics

Alectinib is exempt from the pediatric study requirements of the Pediatric Research Equity Act in accordance with the provisions of 21 CFR 314.55. Alectinib was granted Orphan Drug Designation by the Office of Orphan Products Development for the treatment of ALK-positive non-small cell lung cancer (NSCLC) on January 27, 2015.

11. Other Relevant Regulatory Issues

- *Application Integrity Policy (AIP)*: No Issues
- *Exclusivity or patent issues of concern*: No Issues. Refer to exclusivity review.
- *Financial disclosures*: No Issues. See Dr Larkins' clinical review for Financial Disclosure summary.
- *Other Good Clinical Practice (GCP) issues*: None
- *Office of Scientific Investigations (OSI) audits*:
  From the Clinical Inspection Summary (Drs. Iacono-Connors, Thompson, Ayalew) 11/3/2015: Tumor response data from the Independent Review Committee (IRC) was used to derive the primary efficacy endpoint variable for all patients in Study NP28761 and Study NP28673. The primary efficacy outcome measures reported in the application were corroborated by the source records generated at the clinical sites. There were no trends in underreporting adverse events. Based on the review of preliminary inspectional findings for clinical investigators Dr. Shirish Gadgeel (Site 261586; Study NP28761) and the sponsor of Study NP28761 and NP28673, data submitted to the Agency in support of NDA 208434 appear reliable and can be used in support of the application. The reliability of data for Dr. Sai-Hong Ou's site, associated with Study NP28761 and Study NP28673, submitted to the Agency in support of NDA 208434 cannot be determined until the inspection is completed.
- *Any other outstanding regulatory issues*: None

12. Labeling

Prescribing Information
In addition to staff from the Office of Hematology Oncology Products and the associated review disciplines, consultants from the Office of Prescription Drug Products (OPDP), Office of Surveillance and Epidemiology (OSE), Patient Labeling Team, and Maternal Health Team provided input onto prescribing information.

The following is a high-level summary of prescribing information discussions.

- INDICATIONS AND USAGE section:

- FDA recommended limiting the indication to metastatic (rather than locally advanced) patients, consistent with practice across mNSCLC therapies, and consistent with patient population actually studied.
- At the time of this CDTL review, FDA is still considering whether to include patients who were intolerant of crizotinib, given that there was a paucity of patients in the pivotal studies who discontinued crizotinib due to drug intolerance.
- No Limitation of Use is indicated at this time.

- DOSAGE AND ADMINISTRATION section:
  - I agree with the proposed recommended dosage regimen of 600 mg orally twice daily with food for the indicated patient population
- Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS sections:
  - No BOXED WARNING is indicated at this time.
  - No CONTRAINDICATIONS is indicated at this time.
  - WARNINGS AND PRECAUTIONS: FDA removed the Applicant's proposal to include photosensitivity in this section, as this did not meet the requirements for a WARNING at this time. Photosensitivity is described in section 6, ADVERSE REACTIONS. FDA added a WARNING regarding severe myalgia and creatine phosphokinase (CPK) elevation, given the frequency and severity of this adverse reaction.
- CLINICAL STUDIES section:
  - The proposed studies (NP28761 and NP28673) in this section are adequate and well-controlled and provide primary support for efficacy of the proposed indications
  - Consistent with DOP2/OHOP policy, FDA maintained that ORR should be based on the ITT population, not the response evaluable (RE) population.

Other Labeling

- *Proprietary name*: I concur with DMEPA that the proprietary ALECENSA name is acceptable
- *Patient labeling*: the patient labeling team participated in labeling discussions and provided edits to the patient product insert
- *Carton and container labeling*: DMEPA provided input on carton and container labeling, which after negotiation with the Applicant, was found to be acceptable.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS): The Applicant did not propose a REMS and the review team did not identify the need for a REMS to ensure the safe use of alectinib in the indicated patient population.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

At the time of this approval, FDA determined that the Applicant is required to conduct a PMR study to confirm clinical benefit under the Subpart H Accelerated Approval regulations. The agreed upon PMR is BO28984 (ALEX), an ongoing randomized trial evaluating alectinib versus crizotinib for patients with advanced NSCLC without a history of prior systemic therapy for advanced disease and whose tumors harbor an ALK rearrangement. The final protocol was

submitted in March 2014, and the final report submission will be in June 2018 (final PFS analysis) and final study completion will be March 2019.

In addition, the Applicant must conduct a 505o PMR to complete a pharmacokinetic trial to determine an appropriate dose of alectinib in patients with moderate to severe hepatic impairment.

14. Recommended Comments to the Applicant

None

APPEARS THIS WAY ON ORIGINAL

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

/s/

GIDEON M BLUMENTHAL
11/25/2015