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RESEARCH**

APPLICATION NUMBER:

208434Orig1s000

MEDICAL REVIEW(S)

Addendum to Clinical Review for NDA 208434

This addendum is regarding inclusion of “or intolerant to crizotinib” in the indication for alectinib.

As discussed in the primary Clinical Review of this NDA, there was only one patient among those included in the efficacy assessments for Studies 1 and 2 documented to have discontinued crizotinib because of an adverse event (AE). During labeling negotiations, the Applicant provided additional information on this single phase II patient who was intolerant to crizotinib. In addition, the Applicant provided information on 4 patients enrolled in the Phase 1 part of Study 1 (NP28761) who enrolled onto study following discontinuation of crizotinib because of an AE. The following table, abstracted from information submitted by the Applicant, includes information for each patient on the AEs leading to discontinuation of crizotinib, the best overall radiologic response, and the duration of treatment with alectinib.

Patient	AE leading to crizotinib withdrawal	NP28761 Phase	Alectinib Dose BID	Investigator		IRC	
				BOR	DOR (m)	BOR	DOR (m)
20613	Increased Transaminases	2	600	PR	2.8	PR	2.8
10407	Pneumonitis	1	460	PR	2.8	NA	NA
10411	Increased Transaminases	1	900	SD	NA	NA	NA
10610	Hepatotoxicity	1	600	PR	15.4*	NA	NA
10619	Respiratory Distress	1	900	PR	12.8*	NA	NA

*Censored at the time of primary analysis. 20613 and 10407 discontinued alectinib because of PD (duration of treatment of 4 and 5.5 months respectively). Treatment was ongoing at the time of primary analysis for 10411 (16.1 months), 10610 (17.5 months) and 10619 (15.7 months).

A listing of treatment-emergent AEs experienced by these patients while receiving alectinib was also provided. Two of these patients, both participating in the Phase 1 part of the study, had alectinib dose reduced; one patient had 2 dose reductions, both for Grade 2 neutrophil decreased, and the other patient had dose reduced due to Grade 3 fluid retention. For both of these patients, treatment was ongoing at the time of primary analysis. The majority of AEs were Grade 1-2. Four Grade 3 AEs occurred among 3 of the 5 patients; one patient (Patient 10619) experienced Grade 3 fluid retention and hypokalemia, while Grade 3 hyperglycemia and Grade 3 pain in extremity occurred in one patient each (Patients 10407 and 10411, respectively).

Reviewer comment: Patients 20613 and 10407 discontinued alectinib due to progression of disease after receiving treatment for 4.4 and 5.5 months, respectively. None of these 5 patients discontinued treatment with alectinib due to AE or inability to tolerate therapy. Three of these 5 patients were still receiving treatment with alectinib at the time of primary analysis with durations of treatment exceeding 15 months. While this data involves a small number of patients, based on the available information it is reasonable to include patients intolerant to crizotinib in the indication for alectinib.

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/s/

ERIN A LARKINS
12/09/2015

Clinical Review
 Erin Larkins
 NDA 208434
 Alecensa (alectinib)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208434
Priority or Standard	Priority
Submit Date(s)	July 6, 2015
Received Date(s)	July 6, 2015
PDUFA Goal Date	March 4, 2016
Division/Office	DOP2/OHOP
Reviewer Name(s)	Erin Larkins
Review Completion Date	November 10, 2015
Established Name	Alectinib
(Proposed) Trade Name	Alecensa
Applicant	Hoffmann-La Roche
Formulation(s)	150 mg capsules
Dosing Regimen	600 mg orally twice daily
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) (if applicable)	Treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on crizotinib

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There are no figures included in this review.

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Glossary

AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

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OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Alectinib (proposed proprietary name ALECENSA) is a tyrosine kinase inhibitor that targets ALK and RET. The proposed dosing regimen for alectinib is 600 mg orally twice daily on a continuous schedule using 150 mg capsules. The Applicant's proposed indication for alectinib is "for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib". Alectinib is a new molecular entity (NME).

1.2. Conclusions on the Substantial Evidence of Effectiveness

In the opinion of the reviewer, the submitted evidence meets the statutory evidentiary standard for accelerated approval. The observed objective response rates of 38% and 44% in Study NP28761 and Study NP28673, respectively, are clinically meaningful when considering the intended patient population, patients with ALK-positive NSCLC who have progressed following therapy with the ALK inhibitor crizotinib. The duration of response data, particularly from Study NP28673 which has a longer median duration of follow-up with a median duration of response of 11.9 months, bolsters the assessment of a clinically meaningful benefit for alectinib in this patient population. In addition, the reviewer considers the findings from the pooled analysis of CNS objective response rate (CORR 60.8%) and CNS duration of response (9.1 months) in patients with measurable CNS lesions at baseline clinically meaningful.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Alectinib is a tyrosine kinase inhibitor that targets ALK and RET. The Applicant's proposed indication for alectinib is: "For the treatment of patients with anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib". The Applicant is seeking accelerated approval based on objective response rates and durations of response observed in two single arm studies. My regulatory recommendation is to grant alectinib accelerated approval for the following indication: "For the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic NSCLC who have progressed on crizotinib".

ALK-positive metastatic NSCLC is a life-threatening condition associated with poor survival. Standard first-line therapy for this patient population consists of crizotinib. There is currently no therapy approved for the proposed indication, treatment of patients with metastatic ALK-positive NSCLC who have progressed on crizotinib. Options for treatment of this patient population include the ALK inhibitor ceritinib, which received accelerated approval based on ORR of 44% with a median duration of response of 7.4 months, and chemotherapy, with demonstrated ORRs of 15-45% demonstrated for platinum-based combination chemotherapy. There is an unmet medical need for patients with ALK-positive NSCLC who have progressed on crizotinib.

The observed objective response rates of 38% and 44% in Study NP28761 and Study NP28673, respectively, are clinically meaningful when considering the intended patient population. The duration of response data, particularly from Study NP28673 which has a longer median duration of follow-up with a median duration of response of 11.9 months, bolsters the assessment of a clinically meaningful benefit for alectinib in this patient population. In addition, the reviewer considers the findings from the pooled analysis of CNS objective response rate (CORR 60.8%) and CNS duration of response (9.1 months) in patients with measurable CNS lesions at baseline clinically meaningful.

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. The safety profile of alectinib appears to compare favorably with other therapies currently used in the treatment of this condition, although this assessment is limited by the lack of controlled safety data. The most common adverse reactions were fatigue (41%), constipation (34%), edema (30%), and myalgia (29%). Safety issues identified as significant and serious during the NDA review were hepatotoxicity, interstitial lung disease, bradycardia, and severe myalgia and creatine phosphokinase (CPK) elevation. These safety concerns are adequately addressed by information in the Warnings and Precautions section and the dose modification recommendations included in product labeling. There were no significant safety concerns identified during NDA review

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requiring risk management beyond labeling or warranting consideration for Risk Evaluation and Mitigation Strategy (REMS).

In the opinion of the reviewer, the submitted evidence meets the statutory evidentiary standard for accelerated approval. The observed objective response rates of 38% and 44% in Study NP28761 and Study NP28673, respectively, are clinically meaningful when considering the intended patient population, patients with ALK-positive NSCLC who have progressed following therapy with the ALK inhibitor crizotinib. The duration of response data, particularly from Study NP28673 which has a longer median duration of follow-up with a median duration of response of 11.9 months, bolsters the assessment of a clinically meaningful benefit for alectinib in this patient population. In addition, the reviewer considers the findings from the pooled analysis of CNS objective response rate (CORR 60.8%) and CNS duration of response (9.1 months) in patients with measurable CNS lesions at baseline clinically meaningful. These clinical benefits outweigh the risks associated with alectinib identified during the review of this NDA.

My regulatory recommendation is to grant alectinib accelerated approval for the following indication: “For the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic NSCLC who have progressed on crizotinib”. The removal of “locally advanced” and “intolerant to crizotinib” from the indication proposed by the Applicant are based on a lack of efficacy and safety data for these populations. Of the 225 patients included in the efficacy evaluations in Studies NP28761 and NP28673, 99% had metastatic disease and 99% had discontinued crizotinib due to progression of disease. This recommendation for accelerated approval is based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. Such a confirmatory trial is currently ongoing, assessing alectinib versus crizotinib in the treatment of treatment-naïve patients with ALK-positive advanced NSCLC.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> • Lung cancer is the leading cause of cancer death in the U.S., with more than 85% of all lung cancers classified as NSCLC. • 85% of cases are diagnosed at later stages, and for patients with distant metastasis, the 5-year survival rate is <5%. • Approximately 2-7% of NSCLC tumors harbor ALK rearrangements. 	ALK-positive metastatic NSCLC is a life-threatening condition.
Current Treatment Options	<ul style="list-style-type: none"> • There is currently no therapy indicated specifically for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on crizotinib meeting the criteria of available therapy as defined by the Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics. • A marketed treatment option for patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib is ceritinib, an orally administered ALK inhibitor, which received accelerated approval for this indication in 2014. In the clinical study leading to accelerated approval, the ORR for ceritinib was 44% with a median duration of response of 7.4 months. • Another treatment option for patients with ALK-positive metastatic NSCLC who have progressed on crizotinib is treatment with chemotherapy, which is used for treatment of NSCLC in general, without a specific indication for treatment of ALK-positive NSCLC. ORRs reported for platinum-based combination chemotherapy as first-line therapy for metastatic NSCLC range from 15% to 32%. • In a randomized trial limited to treatment-naïve patients with advanced ALK-positive NSCLC, the ORR in the platinum-based combination chemotherapy arm was 45% with a median progression-free survival of 7.0 months. 	There is an unmet medical need for patients with ALK-positive metastatic NSCLC who experience disease progression on crizotinib. This conclusion is based on the observed response rates and duration of response / progression-free survival reported for therapies currently used in clinical practice for the treatment of this patient population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> There is insufficient data available to determine the potential impact of prior treatment with crizotinib on response to treatment with platinum-based combination chemotherapy. 	
<p><u>Benefit</u></p>	<ul style="list-style-type: none"> The pivotal trials supporting this application, Studies NP28761 and NP28673, are two single arm trials assessing alectinib at a dose of 600 mg BID administered continuously to patients with ALK-positive metastatic NSCLC who have progressed on crizotinib. The primary endpoint for both studies was ORR as assessed by independent central review (IRC). The intent-to-treat populations for efficacy analyses in these 2 studies included 87 and 138 patients, respectively. For NSCLC, ORR may be considered a surrogate endpoint reasonably likely to predict clinical benefit when the treatment effect size is large and the responses are durable (Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics). The observed objective response rates of 38% and 44% in Study NP28761 and Study NP28673, respectively, are clinically meaningful when considering the intended patient population, patients with ALK-positive NSCLC who have progressed following therapy with the ALK inhibitor crizotinib. The duration of response data bolsters the assessment of a clinically meaningful benefit for alectinib in this patient population. With a median duration of follow-up of 4.8 months, the median duration of response in Study NP28761 was 7.5 months. For Study NP28673, which had a longer median duration of follow-up of 10.9 months, the 	<p>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 strengthen the conclusion of a clinically meaningful benefit from treatment with alectinib in the intended patient population.</p> <p>The findings from the pooled analysis of a CNS objective response rate of 60.8% and CNS duration of response of 9.1 months in patients with measurable CNS lesions at baseline are clinically meaningful as well.</p> <p>The high ORR observed with alectinib treatment in the first-line setting in Study AF-001JP provides supportive evidence for the clinical benefit of alectinib observed in Studies NP28761 and NP28673.</p> <p>Based on the demographic and baseline disease characteristics for the patients enrolled</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>median duration of response was 11.9 months.</p> <ul style="list-style-type: none"> • A pooled analysis in patients with measurable CNS lesions at baseline (n=) demonstrated a CNS objective response rate (CORR) of 60.8% and CNS duration of response of 9.1 months. • In the supportive study, Study AF-001JP, examining alectinib treatment in ALK inhibitor-naïve patients with advanced ALK-positive NSCLC, the IRC-evaluated ORR was 93.5%. • A limitation of single arm trials is the potential for known and unknown patient selection bias. 	<p>to Studies NP28761 and NP28673, the overall population in these 2 studies is comparable to the overall U.S. target population. Therefore, the benefit demonstrated in the pivotal studies is expected to extend to the post-market setting.</p>
<p><u>Risk</u></p>	<ul style="list-style-type: none"> • 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. The safety data from these 2 trials is adequate to assess safety with reference to the overall U.S. target population. • Fatal adverse reactions occurred in 2% of patients, and review of these cases does not identify a specific safety concern related to alectinib. • Permanent discontinuation of alectinib due to adverse reactions occurred in only 5% of patients. While 27% of patients had alectinib dosing interrupted for adverse reaction, dose reductions due to adverse reactions occurred in 12% of patients. • 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 	<p>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. The safety profile of alectinib appears to compare favorably with other therapies currently used in the treatment of this condition, although this assessment is limited by the lack of controlled safety data. 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.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>severe myalgia and creatine phosphokinase (CPK) elevation.</p> <ul style="list-style-type: none"> • Grade ≥ 3 elevations of AST, ALT, and or bilirubin occurred in 7% of patients and led to discontinuation of alectinib in 3% of patients. The remaining cases were adequately managed with interruption and/or dose reduction of alectinib. Among patients with elevations of liver function tests, no Hy’s law cases were identified. • ILD occurred in only 1 of 253 patients (0.4%), Grade 3 in severity. • Adverse reaction of bradycardia occurred in 7.5% of patients. All events were Grade 1 or 2 in severity, and the majority of events were not associated with any other AE of clinical relevance. • Grade ≥ 3 myalgia occurred in 1.2% of patients, while Grade ≥ 3 CPK elevation occurred in 4.6%. These events were adequately managed with interruption and/or dose reduction of alectinib. No patient discontinued treatment with alectinib due to myalgia or CPK elevation. There were no cases meeting the definition of rhabdomyolysis as per the criteria of the National Lipid Association guidance. • The safety database does not include a sufficient number of subjects aged 65 and older to determine whether they respond differently from younger subjects. • No important differences are expected in how the drug was studied and administered in the clinical trial versus its expected use in the post-market setting. • Off-label use in patients with non-NSCLC tumors documented to have ALK rearrangement is anticipated, but there are no specific safety concerns related to this potential off-label use in these patients with 	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>life-threatening disease.</p> <ul style="list-style-type: none"> • A limitation of single arm trials is the lack of controlled safety data. 	
<p><u>Risk Management</u></p>	<ul style="list-style-type: none"> • 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. • A clinical PMR is recommended to further assess efficacy of alectinib based on the results of at least one multicenter, randomized clinical trial establishing the superiority of alectinib over available therapy in patients with metastatic ALK-positive NSCLC. • A clinical pharmacology 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). 	<p>Information in the Warnings and Precautions section and the dose modification recommendations included in product labeling adequately address the safety concerns identified during review of this NDA.</p> <p>The clinical PMR is being fulfilled by an ongoing randomized, controlled trial of alectinib versus crizotinib in the treatment of treatment-naïve patients with ALK-positive advanced NSCLC.</p> <p>The clinical pharmacology PMR will be addressed by a pharmacokinetic trial; milestone dates for this study have been provided by the Applicant.</p>

2 Therapeutic Context

2.1. Analysis of Condition

Lung cancer is the leading cause of cancer death in the United States (U.S.), with more than 85% of all lung cancer cases classified as NSCLC. It is estimated that there will be 221,200 new cases of lung and bronchus cancer diagnosed in 2015, with 158,040 deaths due to this disease, representing approximately 27% of all cancer deaths in the U.S.¹ Eighty-five percent of cases are diagnosed at later stages, and for patients with distant metastasis, the 5-year survival rate is less than 5%².

A 2007 article first described the finding that tumors in a small number of NSCLC patients harbored a rearrangement in the anaplastic lymphoma kinase (ALK) gene and the echinoderm microtubule-associated protein-like 4 (EML4) gene (referred to hereafter as ALK rearrangement)³. This ALK rearrangement results in an EML4-ALK fusion protein, a kinase which in preclinical studies demonstrated the potential to result in malignant transformation⁴. ALK kinase inhibitors (hereafter referred to as ALK inhibitors) demonstrated activity against ALK rearrangement-containing cell lines in vitro and in vivo⁵ and against tumors occurring in a transgenic mouse model expressing the EML-ALK fusion protein specifically in lung alveolar epithelial cells⁴.

The estimated incidence of ALK rearrangements in NSCLC tumors is 2-7%⁶. Some patient and tumor factors which appear to be associated with the presence of ALK rearrangement are younger age, light or never smoking status, adenocarcinoma histology, and stage IV disease⁶. Crizotinib, a multi-targeted tyrosine kinase inhibitor, including ALK, was approved in 2011 for the treatment of patients with metastatic NSCLC whose tumors are ALK-positive (i.e., positive for ALK rearrangement). The initial approval of crizotinib was based on early reports from 2 multicenter single arm studies of crizotinib in a total of 255 patients with advanced NSCLC demonstrating objective response rates (ORRs) of 50% and 61%. The majority of patients in these studies had metastatic disease (95%) and had received prior systemic treatment for locally advanced or metastatic disease (94%)⁷. The crizotinib US Prescribing Information (USPI) was later updated with the results of a randomized trial comparing crizotinib to chemotherapy (pemetrexed or docetaxel) in 347 patients with metastatic ALK-positive NSCLC previously treated with one platinum-based chemotherapy regimen which demonstrated an improvement in median progression-free survival (PFS) for patients treated with crizotinib (7.7 months vs 3.0 months; hazard ratio [HR] 0.49 [95% confidence interval {CI} 0.37, 0.64])⁸. The crizotinib USPI was further updated with results from a randomized trial of crizotinib compared to pemetrexed-platinum combination chemotherapy in 343 patients with ALK-positive non-squamous NSCLC who had not received any previous systemic therapy for advanced NSCLC.

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There was a significant improvement in median PFS for patients in the crizotinib arm (10.9 months vs 7.0 months; HR 0.45 [95% CI 0.35, 0.60])⁹, and crizotinib is currently considered standard of care for the first-line therapy of ALK-positive NSCLC¹⁰.

Tumors may develop resistance to crizotinib during treatment; mechanisms of resistance include ALK-dependent resistance occurring due to mutations in the ALK tyrosine kinase domain or activation of alternative signaling pathways¹¹. Another important issue in the treatment of NSCLC is the development of brain metastases. A retrospective analysis of 2 studies assessing crizotinib for the treatment of patients with advanced ALK-positive NSCLC reported that among patients without brain metastases at the time of enrollment on these studies who developed progressive disease, 20% were diagnosed with brain metastases¹².

2.2. Analysis of Current Treatment Options

There is currently no therapy for this specific indication meeting the criteria of available therapy as defined in the Guidance for Industry: Expedited Programs for Serious Conditions - Drugs and Biologics¹³. A marketed treatment option for patients with ALK-positive NSCLC is ceritinib, another orally administered ALK inhibitor, which received accelerated approval in 2014 for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib. Another option in the U.S. for NSCLC patients with progression of disease on crizotinib is treatment with chemotherapy¹⁰, which is used for treatment of NSCLC in general, without a specific indication for treatment of ALK-positive NSCLC.

Ceritinib was granted accelerated approval in 2014 based on ORR and duration of response (DoR) results of a multicenter single arm study in 163 patients with metastatic ALK-positive NSCLC who progressed on or were intolerant to crizotinib. This clinical trial demonstrated an ORR of 44% (95% CI 47%, 62%) as assessed by Blinded Independent Central Review Committee (BIRC) with a median DoR of 7.4 months (95% CI 5.4, 10.1)¹⁴. Approximately 60% of patients initiating treatment with ceritinib at the recommended dose of 750 mg daily required at least one dose reduction, and dose modification related to gastrointestinal toxicities of nausea, vomiting, diarrhea or abdominal pain occurred in 38% of patients¹⁴.

Another treatment considered standard of care in the U.S. for NSCLC patients with progression of disease on crizotinib is chemotherapy, including platinum-based combination chemotherapy in patients who are chemotherapy-naïve¹⁰. Median overall survival (OS) times observed for first-line treatment with platinum-based combination chemotherapy in earlier studies, which included patients with NSCLC regardless of histology, ranged from approximately 8 to 11 months with response rates of 15% to 32%¹⁵. A later randomized study comparing cisplatin plus pemetrexed to cisplatin plus gemcitabine for the first-line treatment of NSCLC demonstrated response rates close to 30% in both arms; this study included a pre-specified analysis of OS by histology, and the median OS for the subset of patients with adenocarcinoma

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receiving cisplatin plus pemetrexed was 12.6 months¹⁶. In a randomized trial comparing crizotinib to platinum-based combination chemotherapy for the first-line treatment of advanced ALK-positive NSCLC, the ORR observed in the chemotherapy arm was 45% with a median progression-free survival (PFS) of 7.0 months¹⁷. These findings are all based on the treatment of patients who have received no prior systemic therapy for advanced NSCLC. Another study randomized patients with ALK-positive NSCLC who had already received one prior platinum-based regimen to treatment with crizotinib versus either pemetrexed or docetaxel and demonstrated ORR of 20% in the chemotherapy arm¹⁸. There is insufficient data available to determine the potential impact of prior treatment with crizotinib on response to treatment with platinum-based combination chemotherapy. Predominant toxicities associated with the chemotherapy regimens most commonly used for NSCLC include hematologic toxicities (e.g., cytopenias), gastrointestinal toxicities (e.g., nausea, vomiting), and neurotoxicity (e.g., peripheral neuropathy with taxanes, ototoxicity with cisplatin).

There is currently an unmet medical need for patients with ALK-positive metastatic NSCLC who experience disease progression on crizotinib.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Alectinib is a new molecular entity (NME) and is not currently marketed in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

IND 111723 for the development of alectinib (AF-802, RO5424802) was filed on 29 September 2011. The initial IND was filed by Chugai Pharma USA, LLC, a U.S. subsidiary of Chugai Pharmaceuticals Co., Ltd (Chugai) based in Japan. Ownership of IND 111723 was transferred from Chugai to Hoffmann-La Roche Inc (Roche), effective as of 11 December 2012. The NDA was filed by Roche. A listing of the pertinent regulatory history for alectinib is included in Table 1. Additional details are provided following this table regarding the justification for Breakthrough Therapy Designation and important agreements that were reached during meetings.

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Table 1: Regulatory History for Alectinib (Reviewer Table)

Date	Description
June 2013	Breakthrough Therapy Designation granted for the development of alectinib for the treatment of ALK-positive NSCLC patients who have progressed on crizotinib therapy
July 2013	Type B post-Breakthrough Therapy Designation meeting
Nov 2013	Type B meeting to discuss the acceptability of the design of Studies NP28761, NP28673, and BO28984 (b) (4) (b) (4)
Dec 2013	Type B pre-phase 3 meeting to discuss the design of the proposed confirmatory trial, Study BO28984, comparing the safety and efficacy of alectinib to crizotinib in the first-line treatment of ALK-positive NSCLC
Sept 2014	Initial Pediatric Study Plan (iPSP) Agreement letter issued.
Sept 2014	Type B meeting to discuss proposed content and format of the clinical section to support filing of the NDA
Nov 2014	Type B meeting to discuss the proposed non-clinical and clinical pharmacology strategy to support filing of the NDA
Jan 2015	Orphan Drug Designation granted for treatment of ALK-positive NSCLC
Mar 2015	Type B pre-NDA meeting to discuss the content and format of the Quality information to be submitted in the NDA, including discussion of the fileability of the (b) (4) % SLS formulation as the commercial formulation
Apr 2015	Type B pre-NDA meeting to discuss the results from Studies NP28761 and NP28673 and to reach agreement on the content and format of the proposed NDA

According to the medical officer review of the Breakthrough Therapy request by Dr. Sean Khozin, Breakthrough Therapy Designation was granted in June 2013 based on the following:

- Preclinical evidence supporting activity in crizotinib-resistant tumors;
- Preliminary evidence of clinical activity in advanced ALK-positive NSCLC patients who have failed crizotinib as demonstrated by ORR of 48% in 21 evaluable patients in an ongoing U.S. phase 1 study (NP28761);
- High response rates (94%) in 46 crizotinib-naïve advanced ALK-positive NSCLC patients

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in an ongoing phase 1-2 Japanese study (AF-001JP), with evidence of durable responses;
and

- Preliminary evidence of activity in patients with CNS metastasis, a common site of relapse in those treated with crizotinib.

Important agreements relevant to clinical review of this NDA reached during meetings between FDA and the Sponsor include the following:

July 2013 Type B post-Breakthrough Therapy Designation meeting

- FDA noted that Roche's proposal to modify the protocol to target an overall response rate of 50% with the lower bound of 35% was acceptable. FDA stated that the results of the trial would be evaluated considering the safety profile of the drug and the durability of response.
- FDA stated that the results would need to demonstrate a substantial advance over available therapy to be considered for accelerated approval under subpart H.
- FDA generally agreed that verification of clinical benefit would be obtained in the randomized, active-controlled trial, Study BO28984.

November 2013 Type B meeting to discuss the acceptability of the design of Studies NP28761, NP28673, and BO28984 (b) (4)

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

April 2015 Type B pre-NDA meeting

- FDA noted that the Study NP28673 and Study NP28761 protocol-defined secondary endpoint of CNS disease control rate (DCR) is unlikely to be included in the label.
- Roche proposed that language be included in product labeling describing the complete response (CR) rate in the CNS, as confirmed by the IRC, in patients with measurable or non-measurable CNS metastases based on a pre-specified exploratory analysis of pooled data from both Study NP28673 and NP28761. FDA agreed to evaluate the proposed language and data supporting this language.

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- FDA agreed that Financial Disclosures are not required for the supporting Japanese study, Study AF-001JP.

3.3. **Foreign Regulatory Actions and Marketing History**

Alectinib was granted marketing approval in Japan on 4 July 2014, under the brand name Alecensa. It is approved for the treatment of “ALK fusion gene-positive unresectable, recurrent or advanced non-small cell lung cancer”. The recommended dose in Japan is 300 mg orally BID, and it is marketed by Chugai in 20 mg and 40 mg capsules to be taken orally. The most recent Development Safety Update Report (DSUR) for alectinib, covering the reporting interval from 4 June 2014 to 3 June 2015, states that post-marketing data that became available from Japan during the reporting interval did not reveal any new, pertinent safety information. During the reporting interval, no safety-related amendments were made to the Japanese label for alectinib or to Chugai’s risk management plan for alectinib based on the post-marketing data.

4 **Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety**

4.1. **Office of Scientific Investigations (OSI)**

For full details, see the Clinical Inspection Summary by Dr. Lauren Iacono-Connors. Two clinical sites were chosen for inspection; these sites were selected based on the number of patients enrolled. The Sponsor was also inspected, with inspection focusing on data from and oversight of 5 study sites (3 for Study NP28761 and 2 for Study NP28673). Inspection results by site are listed in the following table.

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Table 2: Inspection Results by Site (from Clinical Inspection Summary Review)

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

NAI = No deviation from regulations

Interim classifications for clinical inspection site #1 and for the Sponsor inspection were NAI. At clinical inspection site #2, there were some missed protocol-specified periodic assessments and minor documentation issues. The report states that with a few minor exceptions, there was no evidence of underreporting of adverse events. A Form FDA 483 is expected to be issued at the conclusion of this inspection.

Reviewer Comment: The minor issues noted at clinical inspection site #2 would not be expected to have a significant impact on the results of either study.

Final classifications are pending as the above observations are based on preliminary communications provided by the FDA field investigators; EIR has not been received from the field, and complete review of EIR is pending. If conclusions change upon receipt and review of the final EIR, an inspection summary addendum will be generated by OSI.

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4.2. **Product Quality**

See CMC review from current NDA submission. The proposed “to be marketed” 150 mg capsule containing (b) (4) % sodium lauryl sulfate (SLS) (relative to the active ingredient) was the formulation evaluated in the Study NP28673 and in the phase II portion of Study NP28761.

4.3. **Clinical Microbiology**

See CMC review from current NDA submission; there were no Clinical Microbiology concerns.

4.4. **Nonclinical Pharmacology/Toxicology**

See Pharmacology / Toxicology review from current NDA submission by Dr Eias Zahalka and Dr. Kim Ringgold. For discussion of carcinogenicity and effects on reproduction, see Sections 8.7.1 and 8.7.2 of this review, respectively.

4.5. **Clinical Pharmacology**

For full details, see Clinical Pharmacology review from current NDA submission by Dr. Stacy Shord.

4.5.1. **Mechanism of Action**

Alectinib is a tyrosine kinase inhibitor that targets ALK and RET. In nonclinical studies, alectinib inhibited ALK phosphorylation and ALK-mediated activation of the downstream signaling proteins STAT3 and AKT and decreased in vitro tumor cell viability in some cell lines. The major active metabolite of alectinib, M4, has shown similar in vitro potency and activity. Alectinib demonstrated in vitro and in vivo tumor 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 xenograft models implanted with tumors carrying ALK fusion mutations, administration of alectinib resulted in antitumor activity and prolonged survival, including in mouse models implanted with intracranial tumor cell lines.

4.5.2. **Pharmacodynamics**



(b) (4)

The ability of alectinib to prolong the QT interval was assessed in 221 patients administered alectinib 600 mg BID in clinical studies. Alectinib did not prolong the QTc interval to any clinically relevant extent. Two patients had a maximum post-baseline QTcF value of >500 msec or a maximum QTcF change from baseline of >60 msec.

4.5.3. Pharmacokinetics

In patients with ALK-positive NSCLC, the geometric mean (coefficient of variation %) steady-state maximal concentration (C_{max}) for alectinib was 665 ng/mL (44%) and for M4 was 246 ng/mL (45%). The geometric mean steady-state area under the curve (AUC) for alectinib was 7,430 ng*h/mL (46%) and for M4 was 2,810 ng*h/mL. Alectinib exposure is dose proportional across the dose range of 460 mg to 900 mg (i.e., 0.75 to 1.5 times the proposed recommended dose) under fed conditions. Alectinib and M4 reached steady-state concentrations by day 7. The geometric mean accumulation was approximately 6-fold for both alectinib and M4.

Alectinib reached maximal concentrations at 4 hours following administration of alectinib 600 mg BID under fed conditions in patients with ALK-positive NSCLC. The absolute bioavailability was 37% under fed conditions in healthy subjects. A high-fat, high-calorie meal increased the combined exposure of alectinib plus M4 by approximately 3-fold following oral administration of a single dose of alectinib 600 mg in healthy subjects.

(b) (4)

The apparent clearance (CL/F) is 82 L/hour for alectinib and 217 L/hour for M4. The geometric mean elimination half-life for alectinib is 32 hours and for M4 is 31 hours in patients with ALK-positive NSCLC. Alectinib is metabolized by CYP3A4 to its major active circulating metabolite (M4). The geometric mean metabolite/parent exposure ratio at steady-state is 0.40 in patients with ALK-positive NSCLC. M4 is subsequently metabolized by CYP3A4. Following oral administration of a single dose of radiolabeled alectinib under fed conditions in healthy subjects, 98% of the radioactivity was excreted in feces; 84% of the dose was excreted as unchanged alectinib and 6% of the dose was excreted as M4.

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Age, body weight, mild hepatic impairment, mild to moderate renal impairment (creatinine clearance 30 to 89 mL/min), race (White, Asian, and Other) and sex had no clinically important effect on the systemic exposure of alectinib and M4. The pharmacokinetics of alectinib has not been studied in patients with severe renal impairment, end-stage renal disease, or moderate to severe hepatic impairment.

No clinically meaningful effect on the combined exposure of alectinib plus M4 was observed in clinical studies following co-administration of alectinib with a strong CYP3A inhibitor (posaconazole), a strong CYP3A inducer (rifampin), or an acid-reducing agent (esomeprazole). No clinically meaningful effect on the exposure of midazolam (sensitive CYP3A substrate) or repaglinide (sensitive CYP2C8 substrate) is expected following co-administration with alectinib. In vitro studies suggest that alectinib and M4 do not inhibit CYP1A2, 2B6, 2C9, 2C19, or 2D6. In vitro studies suggest alectinib and M4 inhibit P-gp and BCRP but not OATP1B1, OAT1, OAT2, or OCT2 transporter activity.

4.6. **Devices and Companion Diagnostic Issues**

Eligibility for the pivotal studies covered by this review included the requirement for documentation of ALK rearrangement in tumor tissue confirmed by an FDA-approved test. There are no issues of concern related to the use of this test to select patients appropriate for treatment with alectinib.

4.7. **Consumer Study Reviews**

This subsection is not applicable for this review, as alectinib will require a prescription.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 3: Listing of Clinical Trials Relevant to Clinical Review of NDA (Reviewer Table)

Trial Identity	Trial Design	Regimen/ schedule/ route	Primary Endpoint(s)	Median Duration Follow Up	No. of patients enrolled	No. of Centers and Countries
<i>Pivotal Studies to Support Efficacy and Safety</i>						
NP28673	Single arm, phase I/II*, adult patients with advanced ALK-positive NSCLC with PD on crizotinib	600 mg BID orally 28-day treatment cycle	ORR ORR-PC	30.3 weeks (CSR) 47.3 weeks (updated efficacy analysis)	138	56 sites in 16 countries
NP28761	Single arm, phase I/II, adult patients with advanced ALK-positive NSCLC with PD on crizotinib	Phase II: 600 mg BID orally 21-day treatment cycle	Phase I: RP2D Phase II: ORR	20.7 weeks	134	27 sites in 2 countries (26 sites in US, 1 in Canada)
*NP28673 was designed as a phase I/II study, but all patients on this study received 600 mg BID as Study NP28761 had already established this as the RP2D.						
<i>Supportive Study for Efficacy and Safety</i>						
AF-001JP	Single arm, ALK inhibitor-naïve adult patients with advanced ALK-positive NSCLC with PD on prior chemotherapy	300 mg BID orally 21-day treatment cycle	Phase I: DLTs and MTD, safety, and PK Phase II: ORR	14 months	60	13 study sites in Japan

BID, twice daily; DLTs, dose-limiting toxicities; MTD, maximum tolerated dose; ORR, objective response rate; ORR-PC, objective response rate in patients with history of prior chemotherapy; PK, pharmacokinetics; RP2D, recommended phase 2 dose

5.2. Review Strategy

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The clinical review is based on the Clinical Study Reports (CSRs) for the two pivotal studies (NP28673 and NP28761) and the supportive study (AF-001JP) outlined in Section 5.1, as well as the Integrated Summary of Efficacy (ISE), the Integrated Summary of Safety (ISS), and the 90-Day Safety Update Report for alectinib. The clinical review was conducted by Dr. Erin Larkins. A statistical review was conducted by Dr. Huanyu Chen. Among the items reviewed were case report forms (CRFs), selected narratives, primary datasets (for baseline characteristics, efficacy and toxicity submitted by the applicant), study reports for other ALK inhibitor clinical trials in NSCLC, and a literature review of ALK inhibitors studied for the treatment of ALK-positive NSCLC.

Using the primary data from the 2 pivotal studies, the statistician confirmed, and in collaboration with the clinical reviewer, supplemented the Applicant's efficacy analyses. The clinical reviewer confirmed the Applicant's safety analyses of the 2 pivotal studies, conducting analyses of primary data using MedDRA Adverse Event Diagnosis Service (MAED) and JMP programs. Methods used to perform analyses for specific issues (i.e., detailed assessment of a particular safety issue), are explained in the pertinent section of the review. For the supportive study, AF-001JP, the Applicant's analyses are presented with commentary from the clinical reviewer.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study NP28761

6.1.1. Study Design

Overview and Objective

Study NP28761 was entitled "A phase I/II study of the ALK inhibitor CH5424802 in patients with ALK-rearranged non-small cell lung cancer" (Protocol Version 1.0 dated 27 Sep 2011). The objective of the phase I portion of the study was to determine the recommended dose and administration conditions (fasting or non-fasting) of alectinib for use in the phase II portion of the study. The purpose of the phase II portion of the study was to evaluate the efficacy and safety of alectinib at the recommended dose determined from the phase I portion of the study. The primary objective of the phase II portion of the study was to determine the response rate of alectinib in patients with locally advanced or metastatic ALK-positive NSCLC who have failed crizotinib treatment.

Trial Design

The protocol design for NP28761 was a multi-center, open-label, single arm study taking place at North American sites and conducted in two portions, a phase I portion and a phase II portion, 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. Initial enrollment would be to the fasting cohorts. After the highest tolerable dose of alectinib was determined under fasting conditions, patients would be enrolled to non-fasting cohorts. The figures below, abstracted from the protocol, summarize the design and cohort enrollment schedules for the phase I portion of the study; the assessment period for dose-limiting toxicity was Cycle 1 (21 days).

Figure X: NP28761 Fasting Cohort Enrollment Schedule

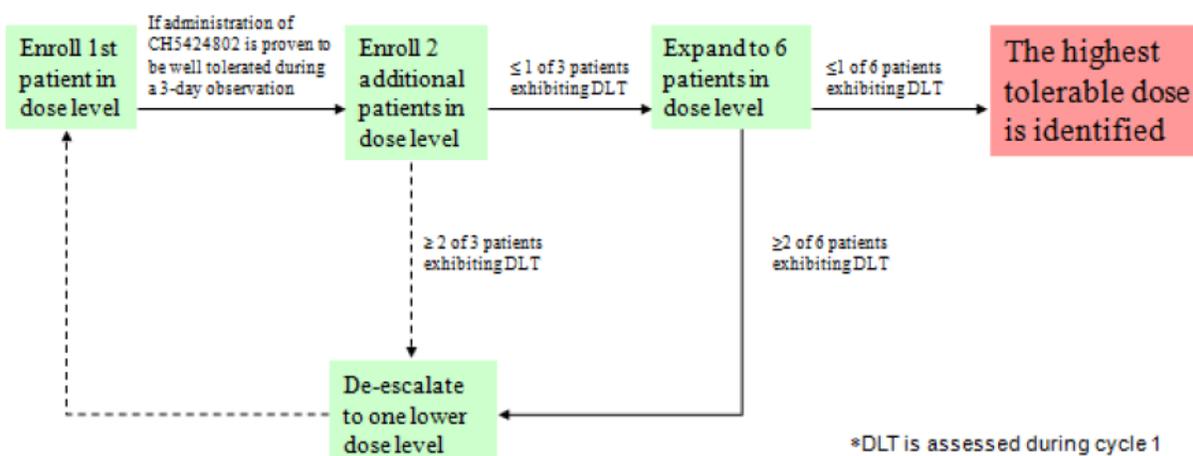
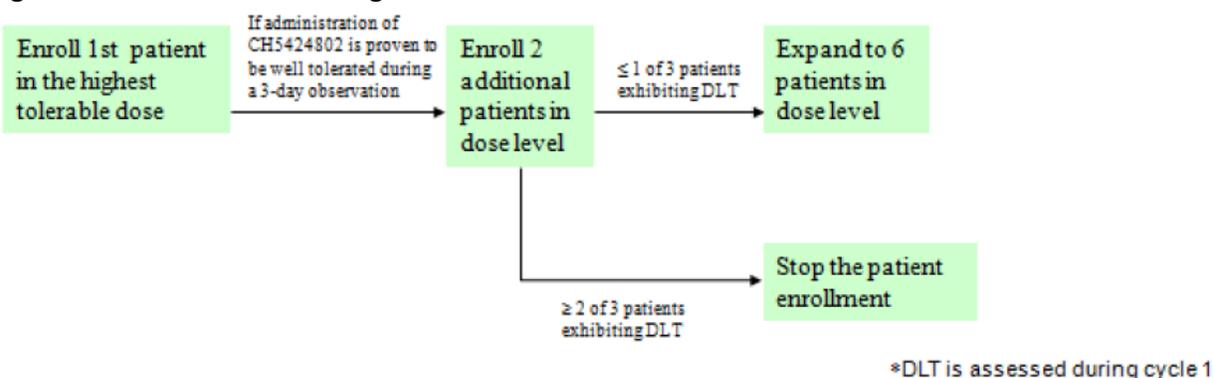


Figure X: NP28761 Non-fasting Cohort Enrollment Schedule



In the phase II portion of NP28761, patients were to be administered alectinib at the recommended dose and administration conditions (fasting or non-fasting) determined from the phase I portion of the study. 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 failed crizotinib treatment (n=49), and Sub-

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population B, consisting of patients who had never received ALK inhibitor treatment (n=15).

Key inclusion criteria

- Pathologically confirmed locally advanced or metastatic NSCLC
- ALK rearrangement confirmed by an FDA-approved test
- Phase I and Sub-population A of phase II: NSCLC that has failed crizotinib treatment
- Sub-population B of phase II: No prior treatment with ALK inhibitor
- Measurable disease defined by RECIST 1.1
- ECOG PS ≤ 2
- Age ≥ 18 years
- Adequate hematologic and organ function, defined as:
 - Absolute neutrophil count (ANC) $\geq 1500/\mu\text{L}$
 - Platelets $\geq 100,000/\mu\text{L}$
 - Hemoglobin ≥ 9.0 g/dL
 - Total bilirubin ≤ 1.5 x the upper limit of normal (ULN)
 - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN (≤ 5 x ULN in patients with liver metastases)
 - Albumin ≥ 2.5 g/dL
 - Serum creatinine ≥ 1.5 x ULN
 - Calculated creatinine clearance ≥ 60 mL/min

Key exclusion criteria

- Prior therapy with ALK inhibitor other than crizotinib
- Not recovered from adverse events or toxicities due to previous treatments to a Grade 1 or less specified in CTCAE v4.0 excepting hemoglobin, albumin, and AST and ALT in patients with liver metastases
- Untreated brain metastases. Patients with brain metastases were eligible if treated with surgery and/or radiation therapy >14 days prior to starting study treatment.
- History of myocardial infarction or stroke within 6 months, congestive heart failure greater than NYHA class II, unstable angina pectoris, cardiac arrhythmia requiring treatment or family history of sudden death from cardiac-related causes
- Known infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV)
- Major surgery within 4 weeks of starting treatment
- Clinically significant gastrointestinal abnormality that would affect the absorption of drug, such as malabsorption syndrome or major resection of the small bowel or stomach.
- Phase I only: Baseline QTc interval duration >470 msec or concomitant use of a drug that prolongs QTc interval
- Phase I only: History of cholecystectomy

The starting dose for Part 1 of NP28673 was selected based on the results of a study conducted in Japan, Study AF-001JP. In the phase I portion of Study AF-001JP, the DLT evaluation for all dose levels was completed under fasting conditions. The initial dose of Study AF-001JP was calculated using the highest non-severely toxic dose (HNSTD) from a 4-week toxicity study in monkeys; extrapolation from animal studies estimated a human half-life of 18.4 hours, resulting in selection of twice daily dosing on a continuous schedule for study in humans. As of a data cut-off date of 29 July 2011, 15 patients were enrolled and the DLT evaluation was completed for 6 dose cohorts (total daily doses of 40, 80, 160, 320, 480, and 600) with alectinib administered twice daily continuously on a 21 day cycle. The maximum dose for Study AF-001JP was set at 600 mg/day (administered as 300 mg twice daily) due to restrictions in Japan on the maximum amount (b) (4) of SLS that can be administered to humans. No DLTs occurred, and there were no deaths on study. Two serious adverse events (AEs) were reported: grade 1 electrocardiogram (ECG) T wave inversion and grade 3 neutrophil count decreased. Activity was demonstrated with partial responses documented at dose levels ranging from 80 mg twice daily to 300 mg twice daily. Plasma exposure (C_{max} and AUC_{0-10}) of alectinib increased approximately dose-proportionally at the dose range of 40 to 600 mg/day in multiple dosing. As there were no DLTs in the phase I portion of Study AF-001JP, a dose of 300 mg twice daily continuously was selected as the starting dose level for NP28761.

The study drug to be used in NP28761 consisted of hard capsules containing 20 or 40 mg of alectinib as free base, along with (b) (4) hydroxypropyl cellulose, sodium lauryl sulfate (SLS), and magnesium stearate. Alectinib was to be administered orally twice daily continuously on a 21 day cycle starting Cycle 1, Day 1 (C1D1). Patients participating in the phase I portion of the study were also to receive a single dose of alectinib for pharmacokinetic measurements, administered on Day -3 of Cycle 1 at a dose of 240 mg for the first 3 patients enrolled (for fasting and non-fasting cohorts) and then for subsequent patients half the daily dose of the dose level assigned (i.e., a single dose of 300 mg on Day -3 for the 300 mg twice daily dose level). For the fasting cohorts, patients were required to fast (only water permitted) for 2 hours before and 1 hour after dose administration. For the non-fasting cohorts, doses were to be taken immediately after breakfast and dinner meals. A high-fat (approximately 50% of total calories) and high-calorie (800 to 1000 calories) meal was recommended as breakfast on Day -3 of Cycle 1, dinner on C1D21, and breakfast on C2D1. Patients in the phase II portion of the study were to be treated with alectinib administered orally twice daily starting C1D1 at the recommended dose and conditions (fasting or non-fasting) determined based on the toxicity profile and pharmacokinetic parameters observed in the phase I portion of NP28761. In order to monitor treatment compliance, the following was documented in the patient's record at each cycle: assigned dose, actual dose taken, dates of administration, pill count (number of capsules dispensed, number of capsules returned), changes in dose and any treatment suspension or discontinuation.

Table 4: Dose Levels for Alectinib Dose Reduction in Study NP28761 (Reviewer Table)

Dose level	Dose (twice daily)
Starting dose	300 mg
-1	240 mg
-2	160 mg
-3	80 mg
-4	40 mg
-5	20 mg

The MTD was defined as the highest dose of alectinib at which no more than 1 of 6 evaluable patients has had a DLT during the first treatment cycle, given that at least 2 patients experienced DLT at the next higher dose level. Grading of AEs was to be determined according to Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0). The following AEs were considered to be DLTs when occurring during the DLT evaluation period (Cycle 1) and a causal relationship to alectinib could not be ruled out by the Investigator:

- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia with bleeding
- Grade 4 neutropenia continuing for ≥ 7 consecutive days
- Non-hematological toxicity of Grade 3 or higher, excluding the following:
 - Transient electrolyte abnormalities
 - Diarrhea, nausea, and vomiting that recovers to Grade 2 or lower with appropriate treatment
 - Patients having Grade 2 AST and/or ALT at baseline must have Grade 3 AST/ALT for 7 days or Grade 4 AST/ALT to be considered a DLT
- Adverse events that required suspension of treatment for a total of ≥ 7 days

Guidelines were provided in the protocol for treatment suspension for AEs occurring during the DLT evaluation period (Cycle 1) in the phase I portion of the study. Alectinib was to be held for the occurrence of any DLT. If the DLT recovered to less than or equal to Grade 1 within 21 days, treatment was to be resumed at the next lower dose level. If the DLT did not recover within 21 days, treatment was to be discontinued. In the event of recurrence of the DLT or worsening of the AE to greater than Grade 3, treatment was to be discontinued. For AEs not meeting the DLT definition, on recovery to less than or equal to Grade 1 or to baseline, treatment was to be resumed at the same dose level.

Dose modification guidelines for the phase II portion of the study and for Cycle 2 onwards in the phase I portion of the study are summarized in the following table. Alectinib could be dose reduced twice, if necessary; if further dose reduction was indicated, treatment with alectinib was to be discontinued.

Table 5: Treatment Suspension and Dose Reduction in the Phase I Portion (Cycle 2 onwards) and the Phase II Portion of Study NP28761 (Applicant Table)

Any of these AEs	
Grade 3 thrombocytopenia w/ bleeding Grade 4 thrombocytopenia Grade 4 neutropenia ≥Grade 3 non-hematological toxicity Excluding the following: <ul style="list-style-type: none"> • Transient electrolyte abnormalities • Diarrhea, nausea, and vomiting that recovers to Grade 2 or lower with appropriate treatment • Grade 3 AST or ALT increased for <7 days in the patients having Grade 2 AST and/or AST at baseline 	
Action	
1 st occurrence	Suspend CH5424802 until the AE recovers to Grade 1 or baseline. If suspension ≤14 days, re-start CH5424802 at same dose. OR If suspension >14 days, re-start CH5424802 with a 1-level dose reduction. OR If suspension >21 days, CH5424802 will be discontinued.
2 nd occurrence	Suspend CH5424802 until AE recovers to Grade 1 or baseline. If suspension ≤21 days, re-start CH5424802 with a 1-level dose reduction. OR If suspension >21 days, CH5424802 will be discontinued.

Use of the following medications was prohibited during the study:

- Chronic immune suppressants
- Drugs that prolong the QTc interval (during the phase I portion only) (see CSR for list)
- CYP3A4 inducers and inhibitors (see CSR for list)
- Proton pump inhibitors and H2 blockers
- Antacids within 2 hours before and 1 hour after the administration of alectinib

Palliative radiation was allowed during the study. If palliative radiation was indicated for brain or bony metastases, dosing of alectinib was to be held for 1 week prior to radiation and for 1 week following radiation.

The following table, abstracted from the protocol, outlines the timing of procedures and evaluations for NP28761.

Table 6: Study Calendar for Study NP28761 (Applicant Table)

Test/Observation day Items within parentheses () are optional.	Screening Within 14 days of first drug administration	Cycle											End of treatment visit -	Safety follow-up 28days after last drug administration	Survival follow-up every 8 weeks
		1						2	3	4	5 and subsequent				
		Day -4	Day -3	Day -2	Day -1	Day 1	Day 8	Day 15	Day 1	Day 1	Day 1	Day 1			
Test/Observation day Allowance (days)	-	-	-	-	-	±2	±2	-3	-3	-3	-3	-3	-	±7	±14
Written informed consent ^{*1}	X														
ALK diagnosis ^{*2}	X														
Drug administration		X													
Record concomitant medications	X	1	1	1	X	X	X	X	X	X	X	X	X		
Vital signs ^{*3}	X		1 ^{*13}		X	X	X	X ^{*13}	X	X	X	X	X		
Physical examination	X		1		X	X	X	X	X	X	X	X	X		
Height	X														
Weight	X		1		X	X	X	X	X	X	X	X	X		
ECOG PS	X		1		X	X	X	X	X	X	X	X	X		
Hematology ^{*4}	X		1		X	X	X	X	X	X	X	X	X		
Chemistry ^{*4}	X		1		X	X	X	X	X	X	X	X	X		
Blood coagulation tests ^{*5}	X		1		X	X	X	X	X	X	X	X	X		
Urnalysis ^{*6}	X		1		X	X	X	X	X	X	X	X	X		
Pregnancy test ^{*7}	X												X		
12-lead ECG	X	1 ^{*14}	1 ^{*14}	1 ^{*14}	2 ^{*14}	2 ^{*14}			X ^{*14}	See footnote ^{*15}			X ^{*14}		
Record AEs ^{*8}										X					
Blood sampling for biomarker ^{*9}			1			2							X		
Blood sampling for pharmacokinetics ^{*10}			1	1	1	X	1	1	X			X		X	
Radiological imaging studies	X ^{*12}									See footnote ^{*16}			X		
EORTC QLQ-C30, QLQ-LC13			1			2				X		X ^{*17}	X		
Tumor core biopsy for ALK Point Mutation ^{*11}	(X)														
Survival															X

X: common for [Phase I portion] and [Phase II portion]; 1: only for [Phase I portion]; 2: only for [Phase II portion]

For footnotes, see CSR.

Treatment with alectinib was to continue until the development of disease progression or unacceptable toxicity. Protocol-specified reasons for early treatment discontinuation included: patient request, pregnancy, investigator decision (i.e., the investigator concludes that it would be inappropriate to continue treatment for some other reason), or Sponsor decision to stop the study.

Replacement of patients considered non-evaluable for the following reasons was allowed in the phase I portion of the study:

- The total dose of alectinib administered was <75% of the prescribed dose for reasons other than DLT or AE.
- Proper DLT/safety evaluation was judged to be difficult because of protocol violation(s), concomitant drug violation, or other significant deviation from protocol.

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The study period was from the date of informed consent until the date of the safety follow-up visit. After completion of the study period, patients were to be followed for survival every 8 weeks from the date of the last dose of alectinib until death, patient is lost to follow-up, or study closure.

An independent review committee (IRC) was established to evaluate radiologic scans for tumor response assessments. Several contract research organizations (CROs) were used in the conduct of NP28761, including for the IRC; for full details see the CSR.

Study Endpoints

The primary objective for the phase I portion of NP28761 was to determine the recommended dose of alectinib for use in the phase II portion of the study, and the primary endpoint was dose-limiting toxicity. Secondary endpoints for the phase I portion of the study were tumor response, quality of life (assessed using EORTC QLQ-C30, QLQ-LC13), safety, and pharmacokinetic parameters.

For the phase II portion of the study, the primary endpoint was response rate in Sub-population A assessed by IRC according to RECIST 1.1 criteria. Response rate is defined as the proportion of responders in the analysis set, where responders are defined as patients determined to have a best overall response of complete response (CR) or PR based on RECIST criteria.

While objective response rates (ORR) have not been demonstrated to reliably predict improvements in survival in NSCLC, responder analyses of patients with NSCLC treated in clinical trials have reported that patients who achieved a response had longer survival compared to non responders^{19, 20}. According to Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics²¹, ORR may be considered a surrogate endpoint reasonably likely to predict clinical benefit when the treatment effect size is large and the responses are durable.

Secondary endpoints for the phase II portion of the study were:

- Response rate in Sub-population B.
- Complete response rate, defined as the proportion of patients with a best overall response of CR.
- Disease control rate (DCR), defined as the proportion of patients with a best overall response of CR, PR, or stable disease (SD) based on RECIST criteria.
- Progression-free survival (PFS), defined as the time from the date of enrollment to the earlier of the date of confirmation of PD through imaging results or the date of death regardless of cause.
- Overall survival (OS), defined as the time from date of enrollment to death regardless of cause.

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- Duration of response, defined as the time from the date the CR or PR was first recorded to the date on which PD is first noted.
- Quality of life, assessed using two instruments, the EORTC QLQ-C30 and QLQ-LC13
- Safety evaluation, performed based on the safety parameters of AEs, laboratory test values (hematology tests, blood chemistry tests, blood coagulation tests, urinalysis), and all medically significant changes (physical findings, vital signs, ECG).
- Pharmacokinetics, consisting of trough value of plasma alectinib concentration for the phase II portion and multiple pharmacokinetic parameters for the phase I portion, including C_{max} , T_{max} , AUC, and $t_{1/2}$.

Statistical Analysis Plan

Please see the Statistical Review by Drs. Huanyu Chen and Kun He for detailed evaluation of the statistical analysis plan.

For the phase I portion of the study, the DLT Evaluation Set was defined as enrolled patients excluding untreated patients and excluding DLT unevaluable patients. Patients could be classified as unevaluable for DLT for the following reasons:

- The total dose of alectinib administered was <75% of the prescribed dose for reasons other than DLT or AE.
- Proper DLT/safety evaluation was judged to be difficult because of protocol violation(s), concomitant drug violation, or other significant deviation from protocol.

Per the protocol, the primary analysis population for efficacy evaluations was to be the intent-to-treat (ITT) population, defined as all enrolled patients excluding untreated patients. This same population was to be used for evaluations of safety (Safety Population [SP]). Additional defined analysis populations were the Per Protocol Set (PPS), defined as the population of patients who comply with the protocol, and an analysis set described as “ITT, excluding ineligible patients, those with protocol deviations, and early discontinuations”.

The null hypothesis (H_0) for NP28761 was a response rate $\leq 10\%$ for Sub-population A, with an assumed alternative hypothesis of a best response rate of 25%. The protocol used a Simon Minimax two-stage design for Sub-population A in the phase II portion of the study, with plans for an interim futility analysis to occur after 23 patients received treatment. Patients treated with the recommended phase II dose in the phase I portion of the trial who met eligibility criteria for Sub-population A could be included in this sub-population. If ≤ 2 responders ($\leq 8.7\%$) were seen, accrual would discontinue; if ≥ 3 responders ($\geq 13.0\%$) were observed the Phase II portion would continue to enroll up to a total of 49 patients. This design provided 80% power at the 0.025 level of significance for a one-sided test. Efficacy evaluations in Sub-population B were to be exploratory in nature.

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The primary analysis set for efficacy endpoints was modified in Version 7.0 of the protocol, dated 17 Dec 2013. According to Version 7.0, the Response Evaluable (RE) population would be used to analyze the primary endpoint of objective response rate (ORR) and other response endpoints (DCR and duration of response). 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 SP was still defined as all patients who received any dose of alectinib, and the SP population was to be used to analyze efficacy endpoints which are not based on response (e.g., PFS, OS). There was no discussion prior to submission of the NDA for alectinib between the Applicant and the FDA regarding this change in the planned primary analysis set.

The principles for handling missing data were defined in the SAP. For duration of response, the last date of “death”, the “last tumor measurement”, “last date in drug log”, or “last follow-up” was used as the censoring date for the patients with no documented progression after CR or PR. For PFS, patients who had neither progressed nor died at the time of the last clinical cut-off or who were lost to follow-up were censored at the last tumor assessment showing no PD either during the study treatment or during follow-up; patients with no post-baseline assessments were censored at the date of first dose. For OS, patients without an event were censored at the date last known to be alive; patients without any follow-up information were censored at the date of first dose. For duration of response, patients who had not progressed or died after having a confirmed response were censored at the date of last tumor measurement.

Assessment of investigator-determined response status was planned as a sensitivity analysis. Preplanned subgroup analyses included assessments of ORR for subgroups based on age, sex, race, baseline ECOG performance status, CNS metastases at baseline, prior exposure to at least one line of platinum-based chemotherapy, and ALK rearrangement confirmed by an FDA approved test.

Protocol Amendments

Key changes to the study design for NP28761 are detailed here.

Protocol Version 2.0, 18 November 2011

There were no significant modifications to the protocol.

Protocol Version 3.0, 14 May 2012

- The design of the phase I portion of the study was modified to include 5 cohorts with a planned enrollment of up to 30 patients. This change also allowed for additional patients to be enrolled beyond 30 if the Sponsor deems it necessary to add patients for determination of the recommended phase II dose.

- A dose escalation scheme was set for the phase I portion of the study. Only the first cohort would be administered alectinib under fasting conditions. Starting with the second cohort, alectinib would be administered under non-fasting conditions.

Table 7: Dose Levels for Alectinib Dose Escalation (Reviewer Table)

Cohort	Twice daily dose
1 (fasting)	300 mg
2 (non-fasting)	460 mg
3 (non-fasting)	600 mg
4 (non-fasting)	760 mg
5 (non-fasting)	900 mg

- The starting time point for the definitions of PFS and OS was changed from the date of enrollment to the data of first administration.

Protocol Version 4.0, 10 August 2012

- The exclusion criterion for brain metastases was modified from: “Untreated brain metastases. Patients with brain metastases will be eligible if treated with surgery and/or radiation therapy >14 days prior to starting the study treatment.” to “Brain metastases, which are symptomatic and/or requiring treatment”. Added “Surgery for brain metastases within 2 weeks of starting treatment” to the exclusion criterion related to major surgery.
- The allowed timing for start of palliative radiation during study treatment was changed to within 24 hours of last dose of alectinib and the criterion for resuming alectinib dosing following palliative radiation was changed to “the resolution of any radiation toxicity to less than or equal to Grade 1”.

Protocol Version 5.0, 8 March 2013

- The title was revised to “A phase I/II study of the ALK inhibitor CH5424802/RO5424802 in patients with ALK-rearranged non-small cell lung cancer previously treated with chemotherapy and crizotinib”.
The term “non-fasting” was replaced with “fed”.
- The primary objective was modified to determination of the response rate in patients “who have failed crizotinib and at least one line of platinum-based chemotherapy treatment”.
- Sub-population B was removed from the protocol as the decision was made not to enroll crizotinib-naïve patients in the phase II portion of the study. References to Sub-population A removed as this now constituted all patients enrolled into the phase II portion of the protocol.
- The following secondary objectives related to CNS relapse were added to the study:

- To assess CNS relapse in patients with brain lesions that were not irradiated.
- To assess CNS relapse rate (CNS PFS).
- An additional cohort was added to the phase I portion of the study, consisting of approximately 6 patients to be enrolled once the MTD was reached in order to evaluate the pharmacokinetics of alectinib following treatment at the recommended phase II dose using 150 mg capsules.
- Planned enrollment in the phase II portion of the study was increased to 85 patients.
- The following changes were made to the definitions for adequate organ function for inclusion in the study:
 - Total bilirubin ≤ 2.0 x ULN in patients with liver metastases
 - AST and ALT ≤ 3 x ULN
 - Serum creatinine ≤ 2 x ULN
- Added the following exception to the exclusion criterion related to brain metastases: “Patients with asymptomatic brain metastasis and clinically stable for at least 2 weeks without steroid treatment are allowed at the treating physician’s discretion.”
- Added the following exclusion criteria:
 - Baseline QTc >470 msec or baseline symptomatic bradycardia <45 beats per minute.
 - Consumption of agents which modulate CYP450 enzymes, transporters, gastric acid altering agents (proton pump inhibitors and/or H2 receptor antagonists), or agents with potential QT prolonging effects within 14 days prior to admission and during the study.
- Replaced the 20 and 40 mg capsules with 150 mg capsules when available. Patients receiving 460 and 760 mg doses will be switched to 450 and 750 mg, respectively, using the 150 mg capsules.
- Allowance made to enable patients in Cohort 1 to switch to fed condition after food effect has been evaluated.
- The null hypothesis used in the statistical plan was modified to a null hypothesis of a best overall response rate of 50%, with the alternative hypothesis a best overall response rate of 65%, with two-sided alpha of 0.05, providing 80% power to reject the null hypothesis with a sample size of 85 patients.
- The plans for the interim futility analysis were modified, including a change to allow continued patient recruitment while awaiting the results of the futility analysis. This analysis would now be conducted after enrollment of 30 patients, and a response rate lower than 30% would cause the study to be terminated.
- Plans to form an Internal Monitoring Committee for the futility analysis were added to the protocol.
- Specific timing was provided for dose administration in the fed state, with doses to be taken within 30 minutes after breakfast or dinner meals.
- Caveat added to allow patients to continue treatment with alectinib in the presence of radiological documentation of PD if, in the investigator’s opinion, there was reasonable

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evidence of ongoing clinical benefit.

Protocol Version 6.0, 24 June 2013

- An exploratory objective was added to assess alectinib CNS penetration by measuring the CSF/plasma concentration ratio, with addition of optional CSF collection to the study.
- Inclusion criterion related to prior crizotinib treatment was modified to specify that the last dose of crizotinib must be within 60 days from signing the Informed Consent Form.
- The term “bridging cohort” was applied to the additional cohort(s) added to the phase I portion of the study to characterize the pharmacokinetics of the recommended phase II dose using 150 mg capsules.
- Option for intra-patient dose escalation was added to the protocol, allowing patients at the previous lower dose cohorts (300, 460, and 760 mg twice daily) to dose escalate and enroll into the bridging cohort(s) after completing at least 3 cycles on their current dose.
- A recommendation was added to advise patients to avoid prolonged sun exposure while taking alectinib and for at least 5 days after study drug discontinuation and to use a broad spectrum sunscreen and lip balm of at least SPF >30 to help protect against potential sunburn.
- A new definition was added to the definitions of analysis sets, the Efficacy Evaluation Set, consisting of the Efficacy Population (EP), defined as patients who received at least one dose of alectinib and who have at least one scan at week 6 or later. The ITT population remained the primary analysis set for efficacy evaluations.

Protocol Version 7.0, 17 December 2013

- The title was revised to “A phase I/II study of the ALK inhibitor CH5424802/RO5424802 in patients with ALK-rearranged non-small cell lung cancer previously treated with crizotinib”.
- The primary objective and other relevant sections of the protocol were modified to reflect the fact that previous treatment with platinum-based chemotherapy was no longer required for study enrollment.
- Language was added to the primary objective to clarify that evaluation of efficacy would be based on the ORR according to RECIST v1.1 as per IRC assessment.
- Assessment of ORR according to RECIST v1.1 as per investigator assessment was added as a secondary objective.
- Secondary objectives and endpoints were modified to indicate that DCR, duration of response, and PFS would be assessed by both IRC and investigator review of radiographs. Complete response rate was removed as a secondary endpoint.
- The pharmacokinetics secondary objective was modified from measurement of the rough concentration of alectinib to characterization of the pharmacokinetics of alectinib and metabolite(s).

- Secondary endpoints related to CNS disease were modified in order to harmonize CNS secondary objectives across the clinical development program:
 - To evaluate CNS objective response rate (CORR) in patients with CNS metastases who have measurable disease in the CNS at baseline, based on IRC review of radiographs by RECIST v1.1 and Response Assessment in Neuro-Oncology (RANO) criteria.
 - To assess CNS duration or response (CDOR) in patients who have a CNS objective response based on IRC review of radiographs by RECIST v1.1 and RANO criteria. To assess CNS progression rates (CPR) at 3, 6, 9, and 12 months based on cumulative incidence by IRC review of radiographs by RECIST v1.1 and RANO criteria.
- The following changes were made to the definitions for adequate organ function for inclusion in the study:
 - Total bilirubin $\leq 2.0 \times$ ULN (regardless of presence of liver metastases)
 - AST and ALT $\leq 2.5 \times$ ULN
 - Removed requirement for albumin ≥ 2.5 g/dL
- The requirement for last dose of crizotinib to have been within 60 days from signing of the Informed Consent form (added in Version 6.0) was removed.
- The exclusion criterion related to brain metastases was modified to provide clarification on eligibility for patients with CNS lesion and to harmonize eligibility criteria across the clinical development program. Patients were excluded for brain or leptomeningeal metastases that are symptomatic and/or require treatment. Patients were to be allowed on study only if the following criteria were met:
 - Patients that have previously been treated with whole brain radiation therapy (WBRT) or gamma-knife radiosurgery must have completed treatment and discontinued the use of corticosteroids for this indication ≥ 2 weeks and any signs and/or symptoms of brain metastases must have been stable for at least 2 weeks prior to first dose of alectinib.
 - Patients that have not previously been treated with whole brain radiation therapy (WBRT) or gamma-knife radiosurgery must have been asymptomatic without neurological signs and clinically stable for ≥ 2 weeks without steroid treatment for CNS metastases prior to the first dose of alectinib.
- The information that the recommended dose for the phase II portion of the study was 600 mg twice daily, based on the results of the phase I portion of the study, was added to the protocol.
- Management guidelines for selected AEs were modified to reflect updates in managing dose reductions and interruptions and to harmonize across alectinib protocols.

Table 8: Guidelines for Managing Selected Adverse Events (Applicant Table)

Event	Action to Be Taken
Abnormal liver function tests and Hepatocellular or Cholestatic damage AE	<p>Liver test laboratory abnormalities are to be reported as AE only if fulfilling the criteria listed in Section 9.2.1.1.</p> <ul style="list-style-type: none"> • If ALT or AST >3x baseline, repeat testing of ALT, AST, Alkaline phosphatase (ALP) and total bilirubin (TBL) within 48-72 hours, with inquiry about symptoms. • At any time during the study treatment, if symptoms compatible with liver injury are observed, liver enzymes should be measured as soon as possible. • Study drug treatment has to be permanently discontinued if any of the following occurs: <ul style="list-style-type: none"> – first observation of ALT or AST >8x ULN – ALT or AST >5xULN for more than 2 weeks – first observation of ALT or AST >3x ULN and TBL >2x ULN – first observation of ALT or AST >3x ULN and the appearance of jaundice or signs of hepatic dysfunction or other symptoms (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia [>5%]). • Following study drug discontinuation, monitoring of laboratory values at weekly intervals should continue until the values have normalized to pre-treatment levels and/or an adequate explanation of the abnormal value is found. • Resumption of study drug is not allowed in patients discontinuing because of any of the above criteria.
Interstitial Lung disease	<ul style="list-style-type: none"> • Patients should be monitored for pulmonary symptoms indicative of pneumonitis. • Study drug should be permanently discontinued in patients diagnosed with pneumonitis/ ILD. • These adverse events represent adverse event of special interest and should be reported immediately to the sponsor (see Section 9.3.3).

Event	Action to Be Taken
QT prolongation	<ul style="list-style-type: none"> • Grade 1 (450-480 ms): no action required • Grade 2 (481 – 500 ms) <ul style="list-style-type: none"> – First and second episode: Continue study medication and monitoring – Third episode: Decrease the current dose of RO5424802 by 150 mg(1 capsule) • Grade 3 (≥ 501 ms on at least two separate ECGs) <ul style="list-style-type: none"> – Temporarily interrupt RO5424802 and refer to a cardiologist – First episode: If improvement to Grade ≤1 or baseline, restart with a dose of 5424802 decreased by 150 mg(1 capsule) – Second episode: If improvement to Grade ≤1 or baseline, restart with a dose of RO5424802 decreased by150 mg (1 capsule) – Third episode: Permanently Discontinue RO5424802 • Grade 4 (≥ 501 ms or > 60ms change from baseline and torsade de pointes or polymorphic ventricular tachycardia or signs/ symptoms of serious arrhythmia) <ul style="list-style-type: none"> – Discontinue RO5424802 permanently and admit patient into the hospital for monitoring
Vision disorders	<ul style="list-style-type: none"> • Events reported as Grade 3 or higher represent adverse events of special interest and should be reported immediately to the sponsor (see Section 9.3.3) • Investigators should consider referring the patients for ophthalmological evaluation according to local clinical practice guidelines, particularly if patients experience photopsia or new or increased vitreous floaters
Skin disorder adverse events (e.g. Phototoxicity, rash)	<ul style="list-style-type: none"> • Patients should be advised to avoid prolonged sun exposure while taking RO5424802 and for at least five days after study drug discontinuation. Patients should also be advised to use a broad spectrum sun screen and lip balm of at least SPF >30 to help protect against potential sunburn.

Event	Action to Be Taken
Hematologic abnormalities	<p>Hematologic laboratory abnormalities are to be reported as AE only if fulfilling the criteria listed in Section 9.2.1.1</p> <ul style="list-style-type: none"> • In case of Hematologic toxicity: Grade 4 (neutropenia, thrombocytopenia): <ul style="list-style-type: none"> – Temporarily interrupt RO5424802 until ANC above 1200/μL, platelet above 75 K/μL. Reduce dose by 150 mg (1 capsule) BID – Give supportive treatment per treating physician. – Reduce dose by another 150 mg (1 capsule) BID after second recurrence – Third episode: Permanently Discontinue RO5424802. • In case of Hematologic toxicity: Grade 3 (neutropenia, thrombocytopenia): <ul style="list-style-type: none"> – Temporarily interrupt RO5424802 until ANC above 1200/μL, platelet above 75 K/μL. – Give supportive treatment. – If improvement to Grade \leq2 does not occur within 3 weeks, permanently Discontinue RO5424802 • In case of Hematologic toxicity: Grade 1 or 2 (neutropenia, thrombocytopenia) no action is required.
Gastrointestinal Tract adverse events (e.g. nausea, vomiting, diarrhea)	<ul style="list-style-type: none"> • The events are expected to be minimized by taking the study drug with meal. In case gastro-intestinal events occur, appropriate measures should be taken in accordance with local clinical practice guidelines. If GI toxicities are observed and not tolerable, treatment with study drug should be temporarily interrupted until recovery to Grade 1 or lower. • Gastrointestinal findings may also be expected from ^{(b) (4)} sodium lauryl sulfate used in the clinical formulation as SLS is a known irritant to GI tract mucosa. • Events reported as Grade 3 or higher represent adverse events of special interest and should be reported immediately to the sponsor. (see Section 9.3.3).

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Event	Action to Be Taken
Abnormal kidney function adverse events	<p>Kidney function laboratory abnormalities are to be reported as AE only if fulfilling the criteria listed in Section 9.2.1.1</p> <ul style="list-style-type: none"> • If at any time during the study treatment serum creatinine increases by $\geq 100\%$ over the baseline visit value, the patient has to be carefully monitored. All the underlying factors that may have acutely impacted serum creatinine levels need to be evaluated and corrected (e.g., dehydration, recent exposure to contrast media, increased amount of cooked meat in diet, concomitant medications affecting renal function as appropriate, etc.). • Any serum creatinine value that is increased by $\geq 100\%$ over the baseline visit value requires repeat testing. • If at the repeat test the serum creatinine value is still $\geq 100\%$ over the baseline visit value, the treatment with RO5424802 should be interrupted. • RO5424802 treatment may be resumed with caution if the serum creatinine value has decreased to approximately the baseline visit value.
Muscular adverse events and/or CPK elevations	<p>CPK laboratory abnormalities are to be reported as AE only if fulfilling the criteria listed in Section 9.2.1.1 of the protocol.</p> <ul style="list-style-type: none"> • Myopathy should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, and/or marked elevations of CPK levels. Patients should promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms. • At any time during the study treatment, the first occurrence of any of the following: <ul style="list-style-type: none"> – asymptomatic CPK values $> 10x$ ULN – symptomatic CPK $> 5x$ ULN – or in the presence of severe muscular symptoms with CPK $> ULN$ although $\leq 5x$ ULN requires monitoring of the CPK values until they are normalized to pre-treatment levels or a reasonable explanation for the CPK elevation and the symptoms is established.

Event	Action to Be Taken
Other toxicities:	<ul style="list-style-type: none"> • <u>Grade 3 or 4</u> <ul style="list-style-type: none"> – Temporarily interrupt RO5424802 for a maximum of 3 weeks. – If improvement to Grade ≤ 1 or baseline does not occur within 3 weeks, permanently discontinue RO5424802. – First episode: If improvement to Grade ≤ 1 or baseline within 21 days, decrease the current dose of RO5424802 by 150 mg (1 capsule) BID. – Second episode: If improvement to Grade ≤ 1 or baseline within 21 days, decrease the current dose of RO5424802 by another 150 mg (1 capsule) BID – Third episode: Permanently discontinue RO5424802. • <u>Grade 2</u> (except nausea, diarrhea, fatigue, or any other symptoms and signs that can be corrected with supportive care) <ul style="list-style-type: none"> – Temporarily interrupt RO5424802 and resume if recovering to \leq Grade 1 or baseline if clinically indicated. – First episode: If improvement to Grade ≤ 1 or baseline within 10 days, continue same dose of RO5424802. If improvement in more than 10 days, decrease the current dose of RO5424802 by 150 mg (1 capsule) BID when resuming treatment. – Second episode: If improvement to Grade ≤ 1 or baseline within 10 days, decrease the current dose of RO5424802 by 150 mg (1 capsule) BID. If improvement in more than 10 days, decrease the current dose of RO5424802 by 300 mg (2 capsules) when resuming treatment. – Third episode: Permanently discontinue RO5424802. • <u>Grade 1</u> <ul style="list-style-type: none"> – no action required

ANC = absolute neutrophil count.

Note: Diarrhea, nausea, and vomiting should be handled with best supportive care first before considering dose modification. Pre-existing pleural effusion will not be considered as an adverse event.

- The following were added to medications/treatments prohibited while on study: ergot derivatives, probenecid, bile acid resins, potent inducers of CYP3A, radiotherapy / radionuclide therapy except for palliative radiotherapy to bone lesions or for pain control.
- The primary analysis population used to analyze the primary endpoint of objective

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response rate (ORR) and other response endpoints (DCR and duration of response) was changed to the Response Evaluable (RE) population, defined as patients with measurable disease at baseline who have a baseline tumor assessment and received at least one dose of alectinib. The ITT population remained the primary analysis set for all other efficacy analyses, such as time-to-event endpoints.

- The null hypothesis used in the statistical plan was modified to a null hypothesis of a best overall response rate of 35%. Per this version of the protocol, with 85 patients, an observed ORR of 46% would have a lower limit of the two-sided 95% CI of 35%, and the null hypothesis would be rejected.
- The Per Protocol Set was removed from the list of analysis sets specified in the protocol.
- A specific plan for the timing of the primary analysis was added to the protocol, with a plan for this to take place once all 85 patients from the phase II portion had been followed for a minimum of 12 weeks (i.e., two tumor assessments).

Data Quality and Integrity: Sponsor's Assurance

Data for NP28761 was captured via an Electronic Data Capture (EDC) System by using electronic case report forms (eCRFs). An eCRF completed by and electronically signed by the principal investigator (PI) or authorized delegate from the study staff was required for each patient enrolled. Per the protocol, investigators were asked that data be entered into the EDC within 3 days (72 hours) of completion of the patient visit. Identification of protocol deviations would be based on information captured on the eCRFs. An audit trail was to maintain a record of initial entries and subsequent changes made and include the following information: reasons for change, time and date of entry, and user name of person making the entry or change.

6.1.2. Study Results

Compliance with Good Clinical Practices

The study report for NP28761 included a statement that the trials were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

Financial Disclosure

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators. The financial disclosure information provided does not raise questions about the integrity of the data. See Appendix 13.2 of this review for details of financial disclosure information.

Patient Disposition

The efficacy results for Study NP28761 are based on a data cut-off date of 24 Oct 2014.

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Phase I

A total of 58 patients were screened for entry into the Phase I portion of the study. 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, as the patient was withdrawn on C1 Day -4 due to symptomatic brain metastasis. At the time of data cut-off, 15 patients (32%) were still on treatment. A total of 32 patients (68%) had withdrawn from treatment, consisting of 9 patients who were still alive, 22 patients who had died, and 1 patient who was lost to follow-up. No patients discontinued treatment prematurely due to AE; the majority of patients were withdrawn due to insufficient therapeutic response (30 patients [64%]), while 2 patient discontinued treatment due to death.

Phase II

A total of 125 patients were screened for entry into the phase II portion of the study. There were 38 screen failures. A total of 87 patients were enrolled, all of whom received at least one dose of alectinib 600 mg. At the time of data cut-off, 56 patients (64%) were still on treatment; 8 of these were receiving treatment beyond progression. A total of 31 patients (36%) had withdrawn from treatment, consisting of 17 patients who were still alive, 12 patients who had died, and 2 patients who were lost to follow-up. The majority of withdrawals were due to insufficient therapeutic response (22 patients [25%]), while 2 patients (2%) were withdrawn due to AE. The reasons reported for withdrawal for the remaining patients were death (n=3), withdrawal by subject (n=2), and other (n=2). The median duration of follow-up was approximately 4.8 months (range 1.1 to 13.7 months).

Protocol Violations/Deviations

Of the 47 patient in the phase I portion of the study, 1 patient had a major protocol violation at baseline of inadequate hematological function; this patient had Grade 3 anemia 3 days before receiving alectinib, which improved to Grade 2 by the time of first dose of alectinib, and no AEs of anemia were reported for this patient during the study. Two patients (4%) had major protocol violations during the study, both due to receipt of prohibited procedures before documented disease progression, one with radiotherapy to the lung and one with craniotomy for a brain lesion. At the time of discovery of these violations, no safety concerns were identified, so the patients were allowed to remain on study; for both, disease progression was confirmed at the next scheduled tumor assessment.

Of the 87 patients in the phase II portion of the study, a major protocol violation occurred in 1 patient at baseline (ALK-positive with a non-FDA approved FISH test); this patient continued to receive alectinib and was not excluded from the study or analyses. During the study, 10 major protocol violations occurred in 8 patients (9%). There were 7 violations in 5 patients due to use of prohibited medications (5 violations) or procedures (2 violations); 4 patients received corticosteroids at dose higher than allowed per protocol, 1 patient received a potent CYP3A4

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inhibitor, 1 patient received radiosurgery to the brain, and 1 patient received radiotherapy to the lung. Two patients had violations due to study drug not taken according to protocol, and 1 patient had a violation due to missing tumor assessment at scheduled visit. At the time of discovery, no safety concerns were identified, all patients continued on study drug as planned, and none of these patients were excluded from any analysis.

Reviewer Comment: Given the nature of these protocol deviations and the small number of each individual type of violation, a significant impact on study outcomes would not be expected.

Table of Demographic Characteristics

Table 9: Demographic Characteristics of Patients in the Phase II Portion of Study NP28761 (Reviewer Table)

Patient Characteristic	N=87
Age (years)	
Mean (SD)	53.6 (11.5)
Median (Range)	54.0 (29-79)
≥65 years (%)	16 (18%)
Race	
White (%)	73 (84%)
Asian (%)	7 (8%)
Other (%)	7 (8%)
Gender	
Female (%)	48 (55%)
Male (%)	39 (45%)
ECOG Performance Status	
0 (%)	30 (35%)
1 (%)	48 (55%)
2 (%)	9 (10%)
Smoking Status	
Non-smoker (%)	54 (62%)
Past smoker (%)	33 (38%)
Active smoker (%)	0 (0%)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 10: Baseline Disease Characteristics for Patients in the Phase II Portion of Study NP28761 (Reviewer Table)

Disease Characteristic	N=87
Stage	
III B (%)	1 (1%)
IV (%)	86 (99%)
Histology	
Adenocarcinoma (%)	82 (94%)
Squamous cell (%)	1 (1%)
Other* (%)	4 (5%)
CNS Metastases	
Measurable + non-measurable	52 (60%)
Measurable	16 (18%)
Prior Systemic Therapy	
Prior platinum-based chemotherapy	61 (70%)
>2 prior regimens (including crizotinib)	64 (74%)
>4 prior regimens (including crizotinib)	27 (31%)
Prior Radiotherapy	
Any radiotherapy for NSCLC	50 (58%)
Radiation therapy for brain metastasis	36 (41%)
Prior Crizotinib	
Time on crizotinib, median (days) (range)	366 (16-1622)
Time since last dose, median (days) (range)	15 (7-733)
ORR with crizotinib	29 (33%)
PD as best response to crizotinib	27 (31%)
Discontinued for reason other than PD	2 (2%)

*Other includes adenosquamous, large cell, and poorly differentiated
 SD, standard deviation; ORR, objective response rate; PD, progressive disease

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Only 2 patients had major protocol violations due to study drug not taken according to protocol. No patients were removed from study or excluded from analyses due to poor compliance.

During the study, 85% of patients in the phase I portion of the study received at least one concomitant medication, including medications used for treatment of AEs. The most common types of medications used were corticosteroids (28% of patients), analgesics (21%), opioid

analgesics (19%), and vitamins and minerals (19%). Among patients in the phase II portion of the study, 83% of patients received at least one concomitant medication during the study, including medications used for the treatment of AEs. The most common types of medications used were laxatives and stool softeners (26% of patients), corticosteroids (21%), and opioid analgesics (21%). One patient was reported as having received concomitant treatment with ceritinib; however, this treatment was initiated after PD, at which time alectinib had already been discontinued.

Efficacy Results – Primary Endpoint

In the phase I portion of Study NP28761 (n=47), the investigator-assessed ORR was 59.6% (95% CI 44.3, 73.6) across all dose cohorts. Responses were observed 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 II portion of Study NP28761.

The primary analysis set for efficacy endpoints in the phase II portion of the study was modified in Version 7.0 of the protocol, dated 17 Dec 2013. According to Version 7.0, the Response Evaluable (RE) population would be used to analyze the primary endpoint of objective response rate (ORR) and other response endpoints (DCR and duration of response). 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 SP was still defined as all patients who received any dose of alectinib, and the SP population was to be used to analyze efficacy endpoints which are not based on response (e.g., PFS, OS). There was no discussion prior to submission of the NDA for alectinib between the Applicant and the FDA regarding this change in the planned primary analysis set.

Efficacy results based on IRC assessments in the RE population were presented for the primary efficacy analysis and were proposed by the Applicant for inclusion in the USPI. Efficacy results based on analysis of the ITT population is more appropriate for inclusion in the USPI. Therefore, efficacy results based on IRC assessment were calculated by the FDA statistical reviewer in the ITT population (see the Statistical Review for the current NDA for details) and confirmed by the Applicant. Results for the primary efficacy endpoint of ORR, along with rates of CR and PR, based on the Applicant's initial assessment in the RE population and based on assessment in the ITT population are presented here. All responses were partial responses.

Table 11: Primary Endpoint Efficacy Results for Study NP28761 (Reviewer Table)

	RE (n=69)	ITT (n=87)
ORR (95% CI)	47.8% (35.6, 60.2)	37.9% (27.7, 49.0)

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Data Quality and Integrity – Reviewers’ Assessment

The primary efficacy analysis was based on IRC review. No trial design or conduct issues that might influence the efficacy results were discovered.

Efficacy Results – Secondary and other relevant endpoints

Applicant analyses of efficacy results for CNS objective response rate (CORR) and CNS duration of response were confirmed by FDA Statistical review. All CNS efficacy results were based on IRC review. Data for the time-to-event endpoints (duration of response, CNS duration of response, PFS, and OS) were immature at the time of data cut-off. However, duration of response is considered a key secondary endpoint for the purposes of this review; therefore estimates of duration of response (as presented by the Applicant and confirmed by FDA Statistical review) are presented here.

- Investigator-assessed ORR (n=87): 46.0% (95 % CI 35.2, 57.0).
- Duration of response: Estimates of median duration of response were based on the 33 patients with an objective response, and were therefore identical for the RE population and the ITT population. With a median duration of follow-up of 4.8 months for Study NP28761, the estimated median duration of response was 7.5 months (95% CI 4.9, not evaluable [NE]).
- CORR in patients with measurable CNS lesions at baseline based on RECIST criteria (n=16): 68.8% (95% CI 41.3, 89.0).
- CNS duration of response: The median CNS duration of response in patients with measurable CNS lesions was not estimable.

Dose/Dose Response

Responses were observed across all dose levels in the phase I portion of the study.

Durability of Response

Duration of response and CNS duration of response are secondary endpoints, and these results are discussed in this section under the subheading of “Efficacy Results – Secondary and other relevant endpoints”.

Persistence of Effect

The available data does not permit an analysis of the effect of drug over time after treatment is

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stopped or withheld.

Additional Analyses Conducted on the Individual Trial

Exploratory analyses conducted by the Applicant included assessment of CORR and CDOR in patients with measurable and non-measurable CNS disease at baseline. These results were confirmed by FDA Statistical review.

- CORR in patients with measurable and non-measurable CNS disease at baseline (n=52): 38.5% (95% CI 25.3, 53.0).
- CNS duration of response: The median CNS duration of response in patients with measurable CNS lesions was not estimable.

6.2. NP28673

6.2.1. Study Design

Overview and Objective

Study NP28673 was entitled “An open-label, non-randomized, multicenter phase I/II trial of RO5424802 given orally to non-small cell lung cancer patients who have ALK mutation and who have failed crizotinib treatment” (Protocol Version 1 dated 12 Dec 2012). The objective of the Part 1 of the study was to determine the recommended phase II dose (RP2D) of alectinib for use in Part 2 the study. The objective of Part 2 of the study was to evaluate the efficacy and safety of alectinib at the RP2D.

Trial Design

The protocol design for NP28673 was a global, multi-center, open-label, single arm study designed to be conducted in three parts – a phase I portion, a phase II portion, and a post-progression treatment portion - in patients with locally advanced or metastatic ALK-positive NSCLC with progression on crizotinib. Part I was designed as a 3+3 dose-escalation to assess the safety, tolerability, and pharmacokinetics of alectinib at dose levels of 600 mg twice daily and 900 mg twice daily with a planned enrollment of up to 12 patients. Enrollment of more than 3 patients per dose level was allowed even without DLT.

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

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on study following progression of disease. Patients whose pre-treatment tumor tissue was positive for epidermal growth factor (EGFR) mutation (e.g., exon 19 deletion or exon 21 L858R) would be offered treatment with a combination of alectinib at the RP2D and erlotinib 100 mg daily. Those with EGFR mutation-negative tumors or unknown EGFR mutation status would be offered continuation of treatment with alectinib if the treating physician considered the patient was receiving clinical benefit from alectinib treatment.

Key inclusion criteria

- Histologically confirmed locally advanced or metastatic NSCLC
- Documented ALK rearrangement based on an FDA-approved test
- Prior treatment with crizotinib and progression based on RECIST v1.1 criteria with the last dose of crizotinib being within 60 days from enrollment. Patients can be either chemotherapy-naïve or have received at least one line of platinum-based chemotherapy.
- Measurable disease defined by RECIST 1.1 criteria
- ECOG PS ≤ 2
- Age ≥ 18 years
- Patients with brain or leptomeningeal metastases are allowed on study if the lesions are asymptomatic without neurological signs and clinically stable for at least 2 weeks without steroid treatment. Patients who do not meet these criteria are not eligible for the study but can be re-screened after completing WBRT. Any corticosteroid therapy must have been completed ≥ 2 weeks prior to the first dose of alectinib.
- Recovery from effects of any major surgery or significant traumatic injury at least 28 days before the first dose of study treatment.
- Adequate hematologic and organ function, defined as:
 - Absolute neutrophil count (ANC) $\geq 1500/\mu\text{L}$
 - Platelets $\geq 100,000/\mu\text{L}$
 - Hemoglobin ≥ 9.0 g/dL
 - Total bilirubin ≤ 2 mg/dL
 - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 2.5 \times \text{ULN}$ ($\leq 5 \times \text{ULN}$ in patients with liver metastases)
 - Serum creatinine $\geq 2 \times \text{ULN}$ or calculated creatinine clearance ≥ 60 mL/min

Key exclusion criteria

- Prior therapy with ALK inhibitor other than crizotinib
- CTCAE v4.03 Grade 3 or higher toxicities due to prior therapy that has not shown improvement and are considered to interfere with current study medication.
- Baseline QTc > 470 msec or baseline symptomatic bradycardia < 45 beats per minute
- Consumption of agents which modulate CYP450 enzymes, transporters, gastric acid altering agents (proton pump inhibitors and/or H2 receptor antagonists), or agents with

potential QT prolonging effects within 14 days prior to admission and during the study.

- Receipt of anticoagulation or thrombolytic agents for therapeutic purposes within 2 weeks prior to Day 1.
- Known HIV positivity or AIDS-related illness.
- Major surgery within 4 weeks of starting treatment.
- Any clinically significant concomitant disease or condition that could interfere with, or for which the treatment might interfere with, the conduct of the study or absorption of oral medications or that would, in the opinion of the Principal Investigator, pose an unacceptable risk to the subject.

The starting dose of 600 mg twice daily for Part 1 of NP28673 was selected based on the preliminary results of Study NP28761. Preliminary data had confirmed the safety of the 300 mg twice daily and 460 mg twice daily doses, and dose escalation in NP28761 was continuing with the next planned dose level of 600 mg twice daily. The study drug to be used in NP28673 consisted of hard capsules including (b) (4) % SLS and supplied as 150 mg capsules. Alectinib was to be administered orally within 30 minutes of a meal twice daily continuously. Treatment compliance was assessed by use of medication diaries, and patients were instructed to return drug containers.

Table 12: Dose Levels Available for Alectinib Dose Reduction in Study NP28673 (Reviewer Table)

Dose level	Dose (twice daily)
Starting dose	600 mg
-1	450 mg
-2	300 mg
-3	150 mg

The MTD was defined as the highest dose of alectinib at which no more than 1 of 6 evaluable patients has had a DLT during the first treatment cycle. Grading of AEs was to be determined according to CTCAE v4.03. The assessment period for DLT was 21 days, and DLT definitions were the same as those used in NP28761, with the addition of neutropenic fever. The doses in this study were not to exceed the MTD from Study NP28761. If a MTD was determined from NP28761, then this dose would be considered the RP2D for NP28673, and no further dose escalations would be considered in NP28673 and Part 1 of this study would repeat assessments for the RP2D in at least 6 patients before beginning Part 2 of the study.

Dose modification guidelines are summarized in the following table.

Table 13: Guidelines for Managing Specific Adverse Events for Study NP28673 (Applicant Table)

Event	Action to Be Taken
Hematologic toxicity: Grade 4 (neutropenia, thrombocytopenia)	<ul style="list-style-type: none"> • Hold all study treatment until ANC above 1200/μL, platelet above 75 K/μL. • Give supportive treatment per treating physician. • Reduce dose by one level after second recurrence. • Third episode: Discontinue all study treatment.
Hematologic toxicity: Grade 3 (neutropenia, thrombocytopenia)	<ul style="list-style-type: none"> • Hold all study treatment until ANC above 1200/μL, platelet above 75 K/μL. • Give supportive treatment. • If improvement to Grade \leq2 does not occur within 3 weeks, discontinue all study treatment.
Hematologic toxicity: Grade 1 or 2 (neutropenia, thrombocytopenia)	<ul style="list-style-type: none"> • No action required.
Other non-hematologic toxicities: Grade 3 or 4	<ul style="list-style-type: none"> • Hold RO5424802 for a maximum of 3 weeks. • If improvement to Grade \leq1 or baseline does not occur within 3 weeks, discontinue RO5424802. • First episode: If improvement to Grade \leq1 or baseline within 21 days, decrease the current dose of RO5424802 by one dose level (150 mg). • Second episode: If improvement to Grade \leq1 or baseline within 21 days, decrease the current dose of RO5424802 by one dose level (i.e. 150 mg). • Third episode: Discontinue RO5424802.
Other non-hematologic toxicities: Grade 2 (except nausea, diarrhea, fatigue, or any other symptoms and signs that can be corrected with supportive care)	<ul style="list-style-type: none"> • Hold all study treatment and resume if recovering to \leqGrade 1 or baseline if clinically indicated. • First episode: If improvement to Grade \leq1 or baseline within 10 days, continue same dose of RO5424802. If improvement in more than 10 days, decrease the current dose of RO5424802 by one level (i.e. 150 mg) when resumes. • Second episode: If improvement to Grade \leq1 or baseline within 10 days, decrease the current dose of RO5424802 by one dose level (i.e. 150 mg). If improvement in more than 10 days, decrease the current dose of RO5424802 by two dose levels (i.e. 300 mg) when resumes. • Third episode: If improved to Grade \leq1 or baseline within 14 days, reduce dose by one level. If not, discontinue RO5424802. • Fourth episode: Discontinue RO5424802.

Use of the following medications was prohibited during the study:

- Systemic immunosuppressive drugs
- Any medications known to affect QT interval duration
- “Potent” inhibitors of CYP3A (see CSR for list)
- Inducers of metabolic enzymes (see CSR for list)
- Substrates of P-glycoprotein transporter or substrates, inhibitors, or inducers of organic anion transporting polypeptide (OATP transporters) (see CSR for list)

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- Anti-secretory agents or any agent with actual or perceived effects on gastric acid and/or gastric pH altering effects, including proton pump inhibitors and H2 receptor antagonists. Intermittent antacid use may be considered in Parts 2 and 3 but will not be allowed on days of pharmacokinetic sampling and must not be within 2 hours of alectinib administration.
- Ergot derivatives, probenecid, and bile acid binding resins

Radiotherapy/radionuclide therapy was prohibited during the study according to the initial version of the protocol.

The following table, abstracted from the protocol, outlines the timing of procedures and evaluations for Part 2 of NP28673.

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Table 14: Study Calendar for Part 2 of Study NP28673 (Applicant Table)

	Screening	Treatment Period										Unplanned Visit ^a	Completion /Early Termination Visit	28-day Follow-Up ^b	Long-term Follow-Up ^c
		Cycle 1				C2	C3	C4	C5	Cx	Cx				
Day	-28 to -1	1	8	15	21	29	57	85	113	141-337	365+				
Informed consent	x														
Demographic data	x														
Detailed medical history and baseline conditions	x														
Fresh tumor Bx (optional) ^d	x ^d														
Vital signs ^e	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Weight	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Height	x														
Brief history and physical examination ^f	x	x				x	x	x	x	x		x	x	x	
Serum pregnancy test ^g	x														
Hematology ^h	x	x				x	x	x	x	x		x	x	x	
Chemistry ⁱ	x	x				x	x	x	x	x		x	x	x	
ECG ^j	x	x ^j		x ^j			x ^j								
Study drug administration		x	x	x	x	x	x	x	x	x	x				
Radiology assessment ^k	x						x		x	x ^k	x ^k	x	x		

	Screening	Treatment Period										Unplanned Visit ^a	Completion /Early Termination Visit	28-day Follow-Up ^b	Long-term Follow-Up ^c
		Cycle 1				C2	C3	C4	C5	Cx	Cx				
Day	-28 to -1	1	8	15	21	29	57	85	113	141-337	365+				
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Other anti-cancer treatments															x
Survival assessment															x
Drug metabolism genotype Sample ^l		x													
PK blood samples ^m		x		x	x	x	x	x	x			x	x		
PD/Predictive biomarkers															
- Archived primary tissue ^d		x ^d													
- Plasma for circulating tumor DNA ⁿ		x													
RCR sample (optional)^o															
- Whole blood for DNA		x													

For footnotes, see CSR.

Treatment with alectinib was to continue until the development of disease progression or unacceptable toxicity. Protocol-specified reasons for early treatment discontinuation included:

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patient request or withdrawal of consent, pregnancy, investigator or Sponsor decision (i.e., the investigator or Sponsor concludes that it would be inappropriate to continue treatment for some other reason), or patient non-compliance (specifically defined as failure to present for clinic visits on 3 occasions without notifying the clinic). In the presence of radiological documentation of PD, patients could continue treatment with alectinib, with or without erlotinib depending on EGFR mutation status, in Part 3 of the study if the treating physician considered the patient was receiving clinical benefit from alectinib treatment.

Patients who discontinued study drug prematurely were not to be replaced. The study period was from the date of informed consent until the date of the study completion/early termination visit. Patients were asked to return to the clinic 28 days after the last dose of study drug for a follow-up visit. After completion of the study period, patients were to be followed for survival via telephone calls and/or clinic visits every 3 months until death, patient is lost to follow-up, or study closure.

An IRC was established to perform independent radiological review of all scans for the final analysis and to determine response and disease progression based on RECIST 1.1 criteria, in addition to local investigator review of radiographs. Several contract research organizations (CROs) were used in the conduct of NP28673, including for the IRC; for full details see the CSR.

Study Endpoints

The primary objectives for Part 1 of NP28673 were: to determine RP2D of alectinib to be used in Part 2 of the study; to evaluate the safety and tolerability of 600 mg and 900 mg (if 900 mg is reached) doses of alectinib administered twice daily for 21 days; to characterize DLTs, if any, associated with these doses; and to characterize the pharmacokinetics of alectinib.

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. ORR is defined as the proportion of patients with confirmed CR or confirmed PR according to RECIST 1.1 criteria relative to the response evaluable (RE) population. Confirmed responses are those that persist on repeat imaging study ≥ 4 weeks after initial documentation of response.

For discussion of response rate as a surrogate endpoint, bolstered by duration of response, see Study Endpoints under Section 6.2.1 of this review.

Secondary endpoints for the phase II portion of the study were:

- ORR based on IRC review using RECIST 1.1 criteria in patients without prior exposure to chemotherapy.

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- Duration of response, defined as the time from the date the CR or PR was first recorded to the date on which PD is first noted or date of death.
- Progression-free survival (PFS), defined as the time from first administration of alectinib to disease progression/relapse or death due to any cause.
- Overall survival (OS), defined as the time from first administration of alectinib to death due to any cause.
- Disease control rate (DCR), defined as CR, PR, and SD at 16 weeks after the first dose of alectinib.
- CNS response rate, defined as the response rate in CNS in the subgroup of patients who has known CNS metastasis but no prior CNS radiation therapy.
- CNS progression rate, defined as the incidence of patients whose CNS lesions have the best ORR of PD by RECIST criteria.
- Safety evaluation, performed based on the safety parameters of AEs, laboratory tests, vital signs, ECGs, and physical examination.
- Pharmacokinetics, including C_{max} , T_{max} , and AUC, as well as population pharmacokinetic analysis to describe the time course of plasma concentrations of alectinib (and/or metabolite[s], if available and appropriate).

The secondary efficacy endpoints were to be assessed for three groups: the overall population, patients with prior exposure to chemotherapy, and patients without prior exposure to chemotherapy.

Statistical Analysis Plan

Please see the Statistical Review by Drs. Huanyu Chen and Kun He for detailed evaluation of the statistical analysis plan.

Per the protocol, the primary analysis population for efficacy evaluations was to be comprised of patients who receive at least one dose of alectinib and who have at least one scan at week 8 or later. Patients from Part 1 treated would contribute to the required sample size. The safety analyses were to include all patients who received at least one dose of study drug.

The null hypothesis (H_0) for NP2863 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 at 8 weeks post-treatment available, by investigator 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

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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 and other response endpoints (DCR and duration of response). 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. All other analyses, including time to event endpoints, would still be performed on the population of patients who received at least one dose of alectinib. There was no discussion prior to submission of the NDA for alectinib between the Applicant and the FDA regarding this change in the planned primary analysis set.

The principles for handling missing data were defined in the protocol. For duration of response, patients who had not progressed or died after having a confirmed response were censored at the date of last tumor measurement. For PFS, patients who had neither progressed nor died were censored at the date of last tumor assessment; patients with no post-baseline assessment were censored at the date of first dose. For OS, patients without an event (death) were censored at the date of last tumor assessment; patients with no baseline tumor assessment were censored at the date of first dose.

Assessment of ORR based on investigator-assessed radiographs using RECIST 1.1 criteria was planned as a sensitivity analysis. Preplanned subgroup analyses (according to a separate statistical analysis plan [SAP]) included assessments of ORR for subgroups based on age, sex, race, baseline ECOG performance status, CNS metastases at baseline, prior exposure to at least one line of platinum-based chemotherapy, and ALK rearrangement confirmed by an FDA approved test.

Protocol Amendments

Key changes to the study design for NP28673 are detailed here.

Protocol Version 2, 21 December 2012

- The exclusion criterion related to use of anticoagulation or thrombolytic agent within 2 weeks prior to Day 1 was removed.

Protocol Version 3, 28 May 2013

- The dose modification for Grade 4 hematologic toxicity was revised to include a dose reduction of one dose level after the first event of Grade 4 neutropenia or thrombocytopenia.

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- A course of action to be taken in case of significant QT/QTc prolongation was added.
- A description of potential class effects of phototoxicity and interstitial lung disease (ILD) were added to the protocol.
- A recommendation was added to advise patients to avoid prolonged sun exposure while taking alectinib and for at least 5 days after study drug discontinuation and to use a broad spectrum sunscreen and lip balm of at least SPF >30 to help protect against potential sunburn.
- To monitor for ILD, SpO2 was added to the vital signs to be collected in the protocol.
- Language was added to clarify that CNS response rate in patients with known CNS metastatic lesions who did not receive prior CNS radiation will be based only on IRC review.
- Specific statements were added indicating that if the RP2D was determined to be 600 mg twice daily (based on ongoing studies), the 900 mg twice daily cohort would not be conducted.
- The inclusion criterion related to brain metastases was modified to also allow re-screening after completion of gamma-knife treatment.

Protocol Version 4, 19 November 2013

- The information that the RP2D has been determined to be 600 mg twice daily based on data obtained from Study NP28761 was added, leading to elimination of plans for a 900 mg twice daily cohort from NP28673 and commencement of Part 2 of the study.
- The restriction for the last dose of crizotinib to be within 60 days from the first dose of alectinib was removed.
- Secondary endpoints related to CNS disease were modified:
 - To evaluate CNS objective response rate (CORR) in patients with CNS metastases who have measurable disease in the CNS at baseline, based on IRC review of radiographs.
 - To assess CNS duration or response (CDOR) in patients with CNS metastases based on IRC review of radiographs.
 - To assess CNS progression rates (CPR) at 3, 6, 9, and 12 months based on cumulative incidence by IRC review of radiographs.
- Modified the plan for evaluation of CNS endpoints to include IRC assessment of scans based on RANO criteria in addition to RECIST criteria.
- A safety outcome measure assessing the effect of alectinib on cardiac repolarization (QTc interval and other ECG parameters) was added.
- The exclusion criterion related to brain metastases was modified. Patients were to be allowed on study if the following criteria were met:
 - Patients that have previously been treated with WBRT or gamma-knife radiosurgery must have completed treatment and discontinued the use of corticosteroids for this indication ≥ 2 weeks and any signs and/or symptoms of brain metastases must have

been stable for at least 2 weeks.

- Patients that have not previously been treated with WBRT or gamma-knife radiosurgery must have been asymptomatic without neurological signs and clinically stable for at least 2 weeks without steroid treatment for brain metastases prior to the first dose of alectinib.
- Creatine phosphokinase (CPK) was added to the list of serum chemistry tests to be performed as part of the study.

Management guidelines for selected AEs were modified to reflect updates in managing dose reductions and interruptions. These guidelines were the same as those added in Version 7.0 of the protocol for Study NP28761 (see

- Table 8 of this review).
- A midazolam drug-drug interaction sub-study to be conducted in approximately 14 additional patients was incorporated into the protocol. These patients were not required to have measurable disease.
- Permitted and prohibited medications were updated based on the available drug-drug interaction information for alectinib. The exclusion criterion related to concomitant medications was modified to the following: “Administration of strong/potent CYP3A inhibitors or inducers (except for oral corticosteroids up to 20 mg prednisolone equivalent per day) or agents with potential QT prolonging effects within 14 days prior to first administration of study drug and while on treatment.” The Prohibited Therapy section of the protocol was updated accordingly.
- The primary analysis population used to analyze the primary endpoint of ORR and other response endpoints (DCR and duration of response) was changed to the Response Evaluable (RE) population, defined as patients with measurable disease at baseline who have a baseline tumor assessment and received at least one dose of alectinib. All other analyses, including time to event endpoints, would still be performed on the population of patients who received at least one dose of alectinib.
- The null hypothesis used in the statistical plan was modified to a null hypothesis of a best overall response rate of 35%. Per this version of the protocol, with 85 patients, an observed ORR of 46% would have a lower limit of the two-sided 95% CI of 35.02%, and the null hypothesis would be rejected. In addition, with 85 patients this would provide 80% power to detect a 15% increase in ORR from 35% to 50% at a 0.05 two-sided significance level. Planned enrollment remained 130 patients, with a maximum of 45 chemotherapy-naïve patients recruited to ensure a minimum number of 85 patients who had received prior chemotherapy.
- A specific plan for the timing of the primary analysis was added to the protocol, with a plan for this to take place once all patients had been followed for a minimum of 16 weeks (i.e., two tumor assessments), unless they progressed or withdrew sooner.

Protocol Version 5, 30 January 2014

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- Protocol Version 4 was not submitted to all countries. For countries where Version 4 was not submitted, the protocol was amended from Version 3 to Version 5, with key changes mirroring those outlined above for Version 4.

Data Quality and Integrity: Sponsor's Assurance

Data for NP28673 was captured via an Electronic Data Capture (EDC) System by using electronic case report forms (eCRFs). An eCRF completed by designated, trained site staff and electronically signed and dated the investigator or a designee was required for each patient enrolled. Study monitors were to perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the CRFs were accurate, complete, and verifiable from source documents. Identification of protocol deviations would be based on information captured on the eCRFs. An audit trail was established to maintain eCRFs and correction documentation.

6.2.2. Study Results

Compliance with Good Clinical Practices

The study report for NP28673 included a statement that the trials were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

Financial Disclosure

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators. The financial disclosure information provided does not raise questions about the integrity of the data. See Appendix 13.2 of this review for details of financial disclosure information.

Patient Disposition

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 (specified where relevant). Submission of these updated efficacy analyses for review was agreed upon between the Applicant and the FDA.

Study NP28673 was initially designed to be conducted in 3 parts. However, during the conduct of Part 1 of the study, the RP2D was confirmed to be 600 mg BID in Study NP28761. Therefore, per protocol, the study moved directly to Part 2 after assessments for the 6 patients in the 600 mg BID cohort of Part 1 were completed. Since the eligibility criteria and schedule of assessments were identical in Parts 1 and 2 (except for pharmacokinetic sampling) and all patients in NP28673 received alectinib at a dose of 600 mg BID, patients from Part 1 were

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merged into Part 2. Part 3 of the study involved treatment of patients from Part 2 of the study after progression of disease on alectinib and, therefore, had no impact the results of the primary analysis of this study.

A total of 176 patients were screened for entry into the phase II 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. At the time of initial data cut-off (18 Aug 2014), 89 of 138 patients (64.5%) were still on treatment; 12 of these were receiving treatment beyond progression. All patients receiving treatment beyond progression in Part 3 of the trial continued treatment with alectinib monotherapy; no patients received treatment with erlotinib in combination with alectinib. A total of 49 patients (35.5%) had withdrawn from treatment, consisting of 25 patients who were still alive and in follow-up and 24 patients who had died. The majority of withdrawals were due to PD (33 patients [24%]), while 10 patients (7%) were withdrawn due to AE. The reasons reported for withdrawal for the remaining patients were death (n=3), physician decision (n=1), withdrawal by subject (n=1), and other (n=1). The median duration of follow-up was approximately 7.0 months (range 0.6 to 12.2 months).

Protocol Violations/Deviations

Of the 138 patients treated in the phase II portion of the study, major protocol violations occurred in 21 patients (15%) at baseline. The majority of these violations were due to ALK status not based on FDA approved test (16 patients [12%]) or not ALK positive (1 patient). Three patients did not meet criteria for adequate hematological, renal, or hepatic function at baseline: 1 due to low neutrophil count, 1 due to elevated ALT, and one due to elevated bilirubin. The remaining protocol violation was due to a positive pregnancy test at baseline, which was subsequently shown to be false positive. During the study, 26 major protocol violations occurred in 23 patients (17%). There were 19 violations in 16 patients due to use of prohibited medications (18 violations) or procedures (1 violation, radiotherapy to a non-target brain lesion). Of the 18 violations related to use of prohibited medications, 9 were due to use of antacids and P-gp substrates; while these were considered prohibited concomitant medications at the time of occurrence, use of these medications was permitted in the latest version of the protocol (Version 5). Six patients had violations due to study drug not taken according to protocol, and 1 patient had a violation due to missing tumor assessment at scheduled visit. All patients continued on study drug as planned, and none of these patients were excluded from any analysis.

Reviewer Comment: Given the description of these protocol deviations, a significant impact on study outcomes would not be expected.

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Table of Demographic Characteristics

Table 15: Demographic Characteristics of Patients in the Phase II Portion of Study NP28673 (Reviewer Table)

Patient Characteristic	N=138
Age (years)	
Mean (SD)	51.5 (11.1)
Median (Range)	52.0 (22-79)
≥65 years (%)	14 (10%)
Race	
White (%)	93 (67%)
Asian (%)	36 (26%)
Other (%)	9 (7%)
Gender	
Female (%)	77 (56%)
Male (%)	61 (44%)
ECOG Performance Status	
0 (%)	44 (32%)
1 (%)	81 (59%)
2 (%)	13 (9%)
Smoking Status	
Non-smoker (%)	96 (70%)
Past smoker (%)	39 (28%)
Active smoker (%)	3 (2%)
Region	
United States (%)	23 (17%)
Western Europe (%)	78 (56%)
Eastern Europe (%)	1 (1%)
Asia (%)	29 (21%)
Australia (%)	7 (5%)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 16: Baseline Characteristics of the Patients in the Phase II Portion of Study NP28673 (Reviewer Table)

Disease Characteristic	N=138
Stage	
IIIB (%)	2 (1%)
IV (%)	136 (99%)
Histology	
Adenocarcinoma (%)	133 (96%)
Squamous cell (%)	0 (0%)
Other* (%)	5 (4%)
CNS Metastases	
Measurable + non-measurable	83 (60%)
Measurable	34 (25%)
Prior Systemic Therapy	
Prior platinum-based chemotherapy	106 (77%)
>2 prior regimens (including crizotinib)	58 (42%)
>4 prior regimens (including crizotinib)	25 (18%)
Prior Radiotherapy	
Any radiotherapy for NSCLC	95 (69%)
Radiation therapy for brain metastasis	69 (50%)
Prior Crizotinib	
Time on crizotinib, median (days) (range)	364 (1-1428)
Time since last dose, median (days) (range)	15 (3-676)
ORR with crizotinib	75 (54%)
PD as best response to crizotinib	27 (20%)
Discontinued for reason other than PD	0 (0%)

*Other includes adenosquamous and large cell
 SD, standard deviation; ORR, objective response rate; PD, progressive disease

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Six of 138 patients (4%) had major protocol violations due to study drug not taken according to protocol. No patients were removed from study or excluded from analyses due to poor compliance.

In Study NP28673, 89% of patients received concomitant medications during the study. The most common types of medications used were analgesics (27% of patients), corticosteroids
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(27%), laxatives and stool softeners (25%), vitamins and minerals (21%), and opioid analgesics (20%).

Efficacy Results - Primary Endpoint

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. Submission of these updated efficacy analyses for review was agreed upon between the Applicant and the FDA.

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 and other response endpoints (DCR and duration of response). 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. All other analyses, including time to event endpoints, would still be performed on the population of patients who received at least one dose of alectinib. There was no discussion prior to submission of the NDA for alectinib between the Applicant and the FDA regarding this change in the planned primary analysis set.

Efficacy results based on IRC assessments in the RE population were presented for the primary efficacy analysis of ORR in all patients and were proposed by the Applicant for inclusion in the USPI. Efficacy results based on analysis of the ITT population is more appropriate for inclusion in the USPI. Therefore, efficacy results based on IRC assessment were calculated by the FDA statistical reviewer in the ITT population (see the Statistical Review for the current NDA for details) and confirmed by the Applicant. Results for the co-primary efficacy endpoints of ORR and ORR in patients with history of prior chemotherapy (ORR-PC, along with rates of CR and PR, based on the Applicant's initial assessment in the RE population and based on assessment in the ITT population are presented here. All responses were partial responses.

Table 17: Primary Endpoint Efficacy Results for Study NP28673 (Reviewer Table)

	All Patients		Patients with Prior Chemotherapy	
	RE (n=122)	ITT (n=138)	RE (n=96)	ITT (n=110)
ORR (95% CI)	50.0% (40.8, 52.9)	44.2% (35.8, 52.9)	43.8% (33.6, 54.3)	39.1% (29.9, 48.9)

Note: For ORR-PC, results in the RE population are based on data cut-off date of 18 Aug 2014, while results in the ITT population are based on data cut-off date of 8 Jan 2015.

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Data Quality and Integrity - Reviewers' Assessment

The primary efficacy analysis was based on IRC review. No trial design or conduct issues that might influence the efficacy results were discovered.

Efficacy Results - Secondary and other relevant endpoints

Applicant analyses of efficacy results for CNS objective response rate (CORR) and CNS duration of response were confirmed by FDA Statistical review. All CNS efficacy results were based on IRC review. Investigator-assessed ORR and ORR-PC are based on data cut-off date of 18 Aug 2014, while CORR and CNS duration of response are based on the updated analysis data cut-off date of 8 Jan 2015. The data for overall survival were still immature at the time of data cut-off for the updated analysis of Study NP28673.

- Investigator-assessed ORR (n=138): 47.8% (95% CI 39.3, 56.5).
- Investigator-assessed ORR-PC (n=110): 46.4% (95% CI 36.8, 56.1).
- Duration of response: Estimates of median duration of response were based on the 61 patients with an objective response, and were therefore identical for the RE population and the ITT population. With a median duration of follow-up of 10.9 months at the time of the updated efficacy analysis for Study NP28673, the estimated median duration of response was 11.2 months (95% CI 9.6, NE). The estimated median duration of response for responders who had received prior chemotherapy (n=43) was 10.9 months (95% CI 9.2, NE).
- CORR in patients with measurable CNS lesions at baseline based on RECIST criteria (n=35): 57.1% (95% CI 39.4, 73.7).
- CNS duration of response: The estimated median CNS duration of response (based on RECIST criteria) in patients with measurable CNS lesions was 9.1 months (95% CI 5.8, NE).
- Progression-free survival: The estimated median PFS was 8.9 months (95% CI 5.6, 11.3).

Reviewer Comment: PFS data is of limited utility in the setting of a single arm trial.

Dose/Dose Response

All patients in Study NP28673 received alectinib at a dose of 600 mg BID.

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Durability of Response

Duration of response and CNS duration of response are secondary endpoints, and these results are discussed under “Efficacy Results – Secondary and other relevant endpoints”.

Persistence of Effect

The available data does not permit an analysis of the effect of drug over time after treatment is stopped or withheld.

Additional Analyses Conducted on the Individual Trial

Exploratory analyses conducted by the Applicant included assessment of CORR and CDOR in patients with measurable and non-measurable CNS disease at baseline. These results were confirmed by FDA Statistical review.

- CORR in patients with measurable and non-measurable CNS disease at baseline (n=84): 42.9% (95% CI 32.1, 54.1).
- CNS duration of response: The estimated median CNS duration of response in patients with measurable and non-measurable CNS disease at baseline was 10.3 months (95% CI 7.6, 11.2).

6.3. AF-001JP

6.3.1. Study Design

Overview and Objective

Study AF-001JP was entitled “Phase I/II study of CH5424802 in patients with non-small cell lung cancer harboring the ALK fusion gene”. The objective of Step 1 of the study was to evaluate the safety, tolerability, and pharmacokinetic parameters of alectinib and to select a RP2D for use in Step 2 of the study. The objective of Step 2 of the study was to evaluate the efficacy and safety of alectinib at the RP2D determined in Step 1 in patients with NSCLC harboring the ALK fusion gene who had received treatment with one or more prior chemotherapy regimens (not including [neo]adjuvant chemotherapy unless NSCLC recurred within 6 months of completion of treatment) and had not received prior treatment with an ALK inhibitor.

Trial Design

AF-001JP was an open-label, multicenter, single arm study conducted in Japan designed with two parts, Step 1 and Step 2. Step 1, with a planned enrollment of 10 to 30 patients, consisted of dose-escalation with assessment of dose-limiting toxicities and a RP2D to be used in Step 2

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of the study. The starting dose for Step 1 was 20 mg twice daily. Alectinib was to be administered under fasting conditions for all patients. In Step 2, patients were to be administered alectinib at the RP2D on a 21 day cycle with radiological tumor assessments once every 3 weeks through Cycle 4 then on subsequent even-numbered cycles (once every 6 weeks). Planned enrollment for Step 2 of the study was 45 patients. Treatment could continue as long as none of the withdrawal criteria were met. Withdrawal criteria were: patient withdrawal, discovery after enrollment that the patient should have been excluded from the study, clear disease progression, continued participation deemed unfeasible due to occurrence of AEs or exacerbation of concurrent disease, pregnancy, investigator decision (i.e., the investigator concludes that continuing treatment would be inappropriate for some other reason).

Key inclusion criteria

- Histologically or cytologically proven NSCLC with ALK fusion gene expression confirmed from tissue or cell sample
- Age ≥ 20 years
- ECOG PS 0-1
- Prior chemotherapy, not including (neo)adjuvant chemotherapy unless NSCLC recurred within 6 months of completing treatment. For Step 1, two or more prior chemotherapy regimens and not amenable to treatment with an existing chemotherapy. For Step 2, one or more prior chemotherapy regimens.
- Measurable disease by RECIST 1.1 criteria (Step 2 only)

Key exclusion criteria

- Prior treatment with an ALK inhibitor
- Cerebral metastases that are symptomatic or require treatment
- Marked prolongation of QTc interval (≥ 450 msec) or concomitant use of a QTc interval-prolonging drug (both for Step 1 only)
- Inability to take oral medication or impaired drug absorption due to a gastrointestinal tract dysfunction or inflammatory bowel disease, etc.
- Ongoing treatment with a steroid preparation (oral or intravenous)
- Pleural effusion, pericardial effusion, or ascites requiring treatment (except when 2 or more weeks have passed since the most recent drainage and no worsening is seen at enrollment)

Study Endpoints

The primary endpoints for Step 1 were DLTs and MTD; safety, based on AEs, laboratory test values, and vital signs; and pharmacokinetics (plasma alectinib concentrations and pharmacokinetic parameters). Tumor response was a secondary endpoint.

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For Step 2, the primary endpoint was IRC-evaluated response rate. Secondary endpoints were:

- Safety based on AEs, laboratory test values, and vital signs
- IRC-evaluated disease control rate (DCR)
- IRC-evaluated progression-free survival (PFS)
- Overall survival
- Pharmacokinetics consisting of plasma alectinib concentrations and pharmacokinetic parameters

Statistical Analysis Plan

Efficacy analyses were to be conducted in the ITT population, defined as the population of enrolled patients excluding untreated patients. The null hypothesis for Step 2 of the study as initially designed was a response rate of $\leq 25\%$. If the null hypothesis with a threshold response rate of 25% evaluated in the first 15 patients in order of enrollment is rejected, then a clinical hypothesis with a threshold response rate of 45% will be tested (null hypothesis of a response rate $\leq 45\%$), in accordance with protocol amendments made in Version 3 of the protocol.

Protocol Amendments

Protocol Version 3 contained a key change to the statistical analysis plan, as detailed in the above paragraph (under Statistical Analysis Plan).

Data Quality and Integrity: Sponsor's Assurance

Data contained in the CRFs for AF-001JP was captured via an Electronic Data Capture (EDC) System. The Sponsor outsourced the following tasks to Chugai Clinical Research Center Co., Ltd.: maintaining a record of any corrections to the data (i.e., date of correction and person who performed it), managing system security, and backing up data appropriately.

6.3.2. Study Results

Compliance with Good Clinical Practices

The study report for AF-001JP included a statement that the trials were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

Financial Disclosure

Financial disclosure information for Study AF-001JP was not included in the NDA. This was agreed upon between the Applicant and the FDA, as AF-001JP is considered a supportive, and not a pivotal study, for purposes of this NDA review.

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Patient Disposition

The data cut-off date for Study AF-001JP was 18 Apr 2013, at which time 1 year had passed since the last enrolled patient started treatment. A total of 24 patients were enrolled in the phase I portion of the study, all of whom received at least one dose of alectinib. At the time of data cut-off, 13 of 24 patients (54.2%) were still on treatment; 11 patients (45.8%) had been withdrawn from the study, all due to PD. A total of 46 patients were enrolled in the phase II portion of the study, all of whom received at least one dose of alectinib 300 mg. At the time of data cut-off, 34 of 46 patients (73.9%) were still on treatment. A total of 12 patients (26.1%) had discontinued treatment, 7 patients (15.2%) due to PD and 5 patients (10.9%) due to AEs.

Protocol Violations/Deviations

Among the 24 patient in the phase I portion of the study, 23 protocol deviations occurred in 12 patients (50.0%). Among the 46 patients in the phase II portion of the study, 38 protocol deviations occurred in 24 patients (52.2%). No patient was discontinued from treatment due to a protocol deviation, and the analysis of the primary efficacy endpoint was based on the ITT population, which included patients with protocol deviations.

Reviewer Comment: A listing of these protocol deviations was reviewed. Based on the nature of these protocol deviations, a significant impact on study outcomes would not be expected.

Table of Demographic Characteristics

Table 18: Demographic Characteristics of the Patients in the Phase II Portion of Study AF-001JP (Reviewer Table)

Patient Characteristic	N=46
Age (years)	
Mean (SD)	49.5 (12.5)
Median (Range)	48.0 (26-75)
≥65 years (%)	4 (9%)
Gender	
Female (%)	24 (52%)
Male (%)	22 (48%)
ECOG Performance Status	
0 (%)	20 (43%)
1 (%)	26 (57%)
Smoking Status	
Non-smoker (%)	27 (59%)
Past smoker (%)	18 (39%)
Active smoker (%)	1 (2%)

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Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 19: Baseline Characteristics of the Patients in the Phase II Portion of Study AF-001JP (Reviewer Table)

Disease Characteristic	N=46
Stage	
III B (%)	2 (4%)
IV (%)	31 (67%)
Post-operative recurrence (%)	13 (28%)
Histology	
Adenocarcinoma (%)	46 (100%)
CNS Metastases	
CNS metastases at baseline	15 (33%)
Prior Chemotherapy	
Prior pemetrexed	36 (78%)
>2 prior regimens	15 (33%)
Only prior regimen neo-adjuvant	1 (2%)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Only 1 patient in the phase I portion of the study, and 6 patients in the phase II portion of the study had protocol deviations due to study drug not taken according to protocol. No patients were removed from study or excluded from analyses due to poor compliance.

During the study, 71% of patients in the phase I portion of the study received at least one concomitant medication. The most common types of medications used were agents affecting digestive organs (42% of patients) and agents affecting the CNS (e.g., benzodiazepines, analgesics, zolpidem) (38%). Among patients in the phase II portion of the study, 83% of patients received at least one concomitant medication during the study. The most common types of medications used were agents affecting digestive organs (48% of patients), agents affecting the CNS (48%), and cardiovascular agents (41%).

Efficacy Results - Primary Endpoint

In the phase I portion of Study AF-001JP, the investigator-assessed ORR among 20 patients with measurable disease at baseline was 90.0% across all dose cohorts. No DLTs occurred up to the highest dose of alectinib used in Step 1, 300 mg BID. Based on safety, pharmacokinetic, and efficacy data, alectinib 300 mg BID was chosen as the RP2D for the phase II portion of Study AF-001JP.

For the phase II portion of the study, the primary endpoint was IRC-evaluated ORR. Among the 46 patients in the phase II portion of the study, the ORR was 93.5% (95% CI 82.1, 98.6),

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including 7 patients (15.2%) with CR and 36 patients (78.3%) with PR.

Reviewer Comment: The high ORR observed in the first-line setting in Study AF-001JP provides supportive evidence for the clinical benefit of alectinib observed in Studies NP28761 and NP28673.

Data Quality and Integrity - Reviewers' Assessment

The primary efficacy analysis was based on IRC review. No trial design or conduct issues that might influence the efficacy results were discovered.

Efficacy Results - Secondary and other relevant endpoints

Secondary efficacy endpoints (with results) for Study AF-001JP were:

- IRC-evaluated DCR: 95.7% (95% CI 85.2, 99.5).
- IRC-evaluated PFS: Median duration of follow-up for PFS was 14.0 months (range 0.6-18.9 months) at the time of data cut-off. Since IRC-evaluated PFS events had occurred in only 7 patients (15.2%) at this time point, it was not possible to estimate median PFS. One-year PFS was estimated to be 83% (95% CI 68, 92).
- Overall survival: Median duration of follow-up for OS was 15.8 months (range 7.6-20.1 months) at the time of data cut-off. At this time point, death had occurred in only 4 of the 46 patients (8.7%) in the phase II portion of the study; therefore, median OS could not be estimated. One-year survival was estimated to be 93% (95% CI 81, 98).

Dose/Dose Response

[Objective responses were observed in patients from Cohort 3 (80 mg BID) onward. In Cohorts 5 (240 mg BID) and 6 (300 mg BID), all patients with measurable disease at baseline by RECIST criteria (7 of 9 patients) achieved a PR.

Durability of Response

Median duration of response was not reported in the CSR for AF-001JP. However, at the time of data cut-off, 1 year had passed since the last enrolled patient started treatment. Among the 46 patients in the phase II portion of the study, 43 patients had achieved a response, and at the time of data cut-off 34 patients were still receiving treatment on study, indicating a significant number of durable responses.

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Persistence of Effect

The available data does not permit an analysis of the effect of drug over time after treatment is stopped or withheld.

Additional Analyses Conducted on the Individual Trial

There are no additional analyses of Study AF-001JP relevant to this review.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

The primary efficacy result most pertinent to this NDA review is ORR as assessed by IRC in the ITT population.

Table 20: Objective Response Rates for the ITT Populations in Studies NP28761 and NP28673 (Reviewer Table)

	NP28761 (n=87)	NP28673 (n=138)
ORR (95% CI)	37.9% (27.7, 49.0)	44.2% (35.8, 52.9)

There was a higher proportion of patients ≥ 65 years old (18% vs 10%), a lower proportion of Asian patients (8% vs 26%), and a slightly lower proportion of non-smokers (62% vs 70%) in Study NP28761 compared to Study NP28673.

Reviewer Comment: The ORR results were similar across these studies.

7.1.2. Secondary and Other Endpoints

Duration of response was considered a key secondary endpoint for this review.

Table 21: Duration of Response for the ITT Populations in Studies NP28761 and NP28673 (Reviewer Table)

	NP28761	NP28673
Number of responders	33	61
Median Duration of Response	7.5 months	11.2 months
95% CI	4.9, NE	9.6, NE
Median Duration of Follow-up	4.8 months	10.9 months

Reviewer Comment: The difference in median durations of response across these trials are most likely attributable to the difference in median duration of follow-up.

Pooled analyses of CORR and CDOR were conducted by the Applicant (and confirmed by FDA Statistics review). CORR and CDOR in patients with measurable CNS lesions at baseline were secondary efficacy endpoints in both studies, while CORR and CDOR In patients with measurable and non-measurable CNS lesions at baseline were exploratory efficacy endpoints.

The table below presents baseline characteristics for patients with CNS lesions at baseline who were included in the pooled efficacy analysis.

Table 22: Baseline Characteristics for Patients with CNS Metastases at Baseline in Studies NP28761 and NP28673 (Reviewer Table)

	NP28761 (n=52)	NP28673 (n=84)
Age: Median (range, yr)	52 (29-75)	50 (22-75)
≥65 years	7 (13%)	6 (7%)
Race: White	45 (87%)	60 (71%)
Asian	4 (8%)	19 (23%)
Female	22 (42%)	48 (57%)
ECOG PS 0	19 (37%)	27 (32%)
1	26 (50%)	48 (57%)
Prior brain radiation	34 (65%)	61 (73%)

Reviewer Comment: With the possible exception of prior brain radiation, these baseline characteristics would not be expected to significantly affect the CNS efficacy endpoints. A higher proportion of patients received prior brain radiation in Study NP28673 compared to NP28761. As this was a subject of interest, the FDA Statistics reviewer conducted an exploratory analysis of CORR and CDOR in patients with and without a history of prior CNS radiation, which is presented below. Even with this imbalance in proportion of patients who received prior brain radiation, the reviewer still considers a pooled analysis of the CNS efficacy data reasonable.

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Results for the individual trials and the pooled analysis are presented here.

Table 23: CNS Objective Response Rate and CNS Duration of Response in Studies NP28761 and NP28673 (Reviewer Table)

	NP28761	NP28673
Number of patients, measurable	16	35
CORR, measurable, % (95% CI)	68.8 (41.3, 89.0)	57.1 (39.4, 73.7)
Pooled analysis (n=51)	60.8 (46.1, 74.2)	
Number of patients, M + NM		
	52	84
CORR, M + NM, % (95% CI)	38.5 (25.3, 53.0)	42.9 (32.1, 54.1)
Pooled analysis (n=136)	41.2 (32.8, 50.0)	
Number of responders		
	11	20
CDOR, measurable, months (95% CI)	NE	9.1 (5.8, NE)
Pooled analysis (n=31)	9.1 (5.8, NE)	
Number of responders		
	20	36
CDOR, M + NM, months (95% CI)	NE	10.3 (7.6, 11.2)
Pooled analysis (n=56)	10.3 (7.6, 11.2)	

CORR = CNS objective response rate; CDOR = CNS duration of response; Measurable = patients with measurable CNS lesions at baseline; M + NM = patients with measurable and non-measurable CNS lesions at baseline; NE = not evaluable

Reviewer Comment: The CORR results were similar across these studies. The CNS duration of response results for the pooled analysis appear to be driven by the results of Study NP28673, which is expected based on longer duration of follow-up for this study.

At the request of the clinical review team, the FDA Statistics reviewer conducted an exploratory analysis of CORR and CDOR in patients with and without a history of prior CNS radiation.

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Table 24: Pooled Analysis of CNS Objective Response Rate and CNS Duration of Response for Patients with and without History of Prior CNS Radiation in Studies NP28761 and NP28673 (Reviewer Table)

	CORR, % (95% CI)	CDOR, months (95% CI)
Measurable		
Prior CNS RT (n=35)	57.1 (39.4, 73.7)	9.2 (5.6, NE)
No prior CNS RT	68.8 (41.3, 89.0)	9.1 (7.1, NE)
M + NM		
Prior CNS RT	33.7 (24.3, 44.1)	9.2 (5.6, NE)
No prior CNS RT	58.4 (42.1, 73.7)	10.3 (9.1, 11.0)

CNS RT = prior CNS radiation; CORR = CNS objective response rate; CDOR = CNS duration of response; Measurable = patients with measurable CNS lesions at baseline; N + NM = patients with measurable and non-measurable CNS lesions at baseline; NE = not evaluable

Reviewer Comment: CNS responses were observed in both patients who had and had not received prior CNS radiation, and CNS duration of response was similar across these subgroups.

7.1.3. Subpopulations

Subgroup analysis of ORR in by the baseline demographic characteristics of age, race, and sex were conducted and presented in the Statistical Review for this NDA.

Table 25: Subgroup Analyses of ORR per IRC Assessment (Reviewer Table, adapted from FDA Statistics Reviewer Table)

	NP28761	NP28673
	% (95% CI)	% (95% CI)
ITT population	37.9 (27.7, 49.0)	44.2 (35.8, 52.9)
Age		
<65 years	35.2 (24.2, 47.5)	45.2 (36.2, 54.4)
≥65 years	50.0 (24.7, 75.4)	35.7 (12.8, 64.9)
Race		
White	38.4 (27.2, 50.5)	43.0 (32.8, 53.7)
Asian	57.1 (18.4, 90.1)	50.0 (32.9, 67.1)
Other	14.3 (0.3, 57.9)	33.3 (7.5, 70.1)
Sex		
Female	35.4 (22.2, 50.5)	41.6 (30.4, 53.4)
Male	41.2 (35.6, 57.9)	47.5 (34.6, 60.7)

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Reviewer Comment: Responses were noted in all subgroups. Comparisons between response rates for these subgroups are not meaningful given the relatively small numbers of patients and the wide confidence intervals.

7.1.4. Dose and Dose-Response

The exposure-response relationship appeared flat for best overall response and CNS best overall response (see Clinical Pharmacology review from current NDA submission for details). Responses were observed across all dose cohorts in the phase I portion of Study NP28761.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

See Section 7.1.2 of this review for duration of response data.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

There are no efficacy concerns regarding potential differences in efficacy in subpopulations or regarding potential differences in how the drug was administered and used in the clinical trials versus its expected use in the postmarket setting.

7.2.2. Other Relevant Benefits

Relevant benefits are covered in other areas of this review.

7.3. Integrated Assessment of Effectiveness

In the opinion of the reviewer, the submitted evidence meets the statutory evidentiary standard for accelerated approval. The observed objective response rates of 38% and 44% in Study NP28761 and NP28673, respectively, are clinically meaningful when considering the intended patient population, patients with ALK-positive NSCLC who have progressed following therapy with a the ALK inhibitor crizotinib. The duration of response data, particularly from Study NP28673 which has a longer median duration of follow-up with a median duration of response of 11.9 months, bolsters the assessment of a clinically meaningful benefit for alectinib in this patient population. In addition, the reviewer considers the findings from the pooled analysis of CNS objective response rate (CORR 60.8%) and CNS duration of response (9.1 months) in patients with measurable CNS lesions at baseline clinically meaningful.

The efficacy results included in the label should include ORR and duration of response data as assessed by IRC for the ITT population from each of the pivotal studies (NP28761 and NP28673). It would also be appropriate to include the results from the pooled analysis of CORR and CNS duration of response in the label.

8 Review of Safety

8.1. Safety Review Approach

The clinical reviewer confirmed the Applicant's safety analyses of the two pivotal studies, NP28761 and NP28673, conducting analyses of primary data using MedDRA Adverse Event Diagnosis Service (MAED) and JMP programs. Key safety issues identified for more detailed review include bradycardia, interstitial lung disease, elevations of transaminases and bilirubin, and elevation of CPK and myalgia. Methods used to perform analyses for specific issues (i.e., detailed assessment of a particular safety issue), are detailed in the pertinent section of the review.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Across the two pivotal trials, NP28761 and NP28673, a total of 253 patients were exposed to alectinib at a dose of 600 mg BID. The maximum dose of alectinib used in the supportive study, AF-001JP, was 300 mg BID.

Table 26: Safety Population (Reviewer Table)

Safety Database for Alectinib 600 mg BID Individuals exposed to alectinib 600 mg BID in this development program for the indication under review N=253			
Clinical Trial Groups	Phase I (n=13)	Phase II (n=225)	Midazolam Sub-study (n= 15)
NP28761	13	87	0
NP28673	0	138	15

The median duration of exposure for these 253 patients was 40.6 weeks (range 0.1-114.0 weeks) at the time of the data cut-off for the 90-Day Safety Update Report (27 Apr 2015).

Table 27: Duration of Exposure (Reviewer Table)

Number of patients exposed to the study drug:		
>24 weeks	>52 weeks	>76 weeks
N=177	N=100	N=16

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8.2.2. Relevant characteristics of the safety population:

Table 28: Patient Characteristics for the Safety Population (Reviewer Table)

Patient Characteristic	N=253
Age (years)	
Mean (SD)	52.6 (11.3)
Median (Range)	53.0 (22-81)
≥65 years (%)	36 (14.2%)
Race*	
White (%)	186 (73.5%)
Asian (%)	46 (18.2%)
Other (%)	17 (6.7%)
Gender	
Female (%)	138 (54.5%)
Male (%)	115 (45.5%)
ECOG Performance Status	
0 (%)	88 (34.8%)
1 (%)	142 (56.1%)
2 (%)	23 (9.1%)
Smoking Status	
Non-smoker (%)	171 (67.6%)
Past smoker (%)	78 (30.8%)
Active smoker (%)	4 (1.6%)

*Race reported as "Unknown" for 4 patients

Table 29: Baseline Disease Characteristics for the Safety Population (Reviewer Table)

Disease Characteristic	N=253
Stage	
IIIB (%)	3 (1.2%)
IV (%)	250 (98.8%)
Histology	
Adenocarcinoma (%)	242 (95.6%)
Squamous cell (%)	1 (0.4%)
Other* (%)	10 (4.0%)
CNS Metastases	
CNS metastases at baseline	135 (53.4%)
Prior Systemic Therapy	
Prior platinum-based chemotherapy	(75%)
>2 prior regimens (including crizotinib)	135 (53.3%)
>4 prior regimens (including crizotinib)	61 (24.1%)
Prior Radiotherapy	
Any radiotherapy for NSCLC	159 (62.8%)
Radiation therapy for brain metastasis	119 (47.0%)
Prior Crizotinib	
Time on crizotinib, median (days) (range)	372 (1-1622)
Time since last dose, median (days) (range)	15 (7-733)
ORR with crizotinib	115 (45.5%)
PD as best response to crizotinib	58 (22.9%)
Discontinued for reason other than PD	2 (0.8%)

*Other includes adenosquamous, large cell, and poorly differentiated
 SD, standard deviation; ORR, objective response rate; PD, progressive disease

8.2.3. Adequacy of the safety database:

The safety data from these two trials is adequate to assess safety with reference to the overall U.S. target population. The safety database does not include a sufficient number of subjects aged 65 and older to determine whether they respond differently from younger subjects.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

This submission was of adequate quality for clinical review. There are no concerns regarding the integrity of the submission.

8.3.2. Categorization of Adverse Events

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The definitions of AE and SAE provided in the protocols were appropriate. The AE collection period for both studies was from the date of start of treatment with alectinib until 28 days after the final administration or until the day of study completion for patients who finish the study for reasons such as the start of subsequent treatment for NSCLC before 28 days after the final administration. SAEs considered related to study drug were collected indefinitely.

AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 17.0 and assessed by frequency; preferred terms were assigned by the Sponsor to the original terms entered on case report form. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 was used to grade AEs.

The Applicant summarized AEs by preferred term. Overall, this is appropriate for this application, although this method may create a “splitting” effect for some AE terms. There was one relevant example of splitting in this application, listing “fatigue” and “asthenia” under the preferred terms rather than grouping them together. The potential for splitting was mitigated in the Applicant’s analysis of selected AEs (AEs of special interest) by the use of SOCs, SMQs, combined HGLTs, or combined preferred terms to define these selected AEs.

Based on potential risks identified from non-clinical and clinical studies of alectinib, as well as known safety data on other ALK inhibitors, selected AEs were defined in the protocols for Study NP28761 and Study NP28673. The majority of these selected AEs were based on grouping AE terms by Standardized MedDRA queries (SMQs) and/or System Organ Classes (SOCs) and included the following:

- GI AEs (e.g., nausea, vomiting, diarrhea), SOC Gastrointestinal disorders
- Hepatocellular or cholestatic damage AE and abnormal liver function test (LFTs), SMQ Drug related hepatic disorder, narrow, comprehensive
- Interstitial lung disease (ILD), SMQ Interstitial lung disease, narrow
- QT interval prolongation, SMQ Torsade de pointes QT prolongation, narrow
- Vision disorders, SOC Eye disorders
- Skin disorders (e.g., phototoxicity AEs, rash), SOC Skin and subcutaneous tissue disorders
- Hematologic abnormalities, SMQ Hematopoietic cytopenias, wide
- Muscular AEs and CPK elevations, High Level Group Term (HLGT) Musculoskeletal and connective tissue disorders not elsewhere classified (NEC), HLGT Muscle disorders, HLGT Enzyme investigations NEC (from SOC investigations)
- Abnormal kidney function AEs (e.g., serum creatinine increase, renal impairment, renal failure), SOC Renal and urinary disorders, HLGT Renal and urinary tract investigations and urinalyses, SMQ Acute renal failure, narrow

In addition to these selected AEs, two other AEs of relevance identified by the Applicant based

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on data from Studies NP28761 and NP28673 and were analyzed. The definitions for these AEs were:

- Bradycardia, Preferred Terms bradycardia and sinus bradycardia
- Edema, Preferred Terms edema peripheral, edema, generalized edema, periorbital edema, and eyelid edema

The safety assessment methods used by the Applicant seem adequate for the population, disease, and indication being investigated.

8.3.3. Routine Clinical Tests

The tests conducted as part of routine clinical testing and the frequency of such testing are detailed in the Study Calendars are included in Sections 6.1.1 and 6.2.1 of this review. Relevant to this NDA review, CPK was included as part of routine clinical testing in Study NP28761 from the start of the study but was not added as part of routine clinical testing in Study NP28673 until the amendment for Protocol Version 4 (dated 19 Nov 2013).

Per protocol for both studies, laboratory abnormalities were to be reported as AEs if meeting any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in medical intervention or change in concomitant therapy
- Clinically significant in the investigator's judgment

The protocol for Study NP28761 included the following additional criterion: "Any laboratory abnormalities determined to be related to any SAEs".

In addition to providing information on laboratory test abnormalities reported as AEs, the Applicant provided laboratory shift tables for clinically relevant laboratory results, with data available for 250 of the 253 patients included in the ISS, with the exception of CPK for which data was available for 218 patients.

The safety assessment methods and time points described in the protocols seem adequate for the population, disease, and indication being investigated.

8.4. Safety Results

8.4.1. Deaths

Overall, 74 of 253 patients (29%) included in the ISS had died by the time of the data cut-off for the 90-Day Safety Update Report, with the majority of deaths due to disease progression (67 of 74 patients [92%]). Only 7 deaths on study among 253 patients (2.8%) were attributed to causes other than disease progression, with the cause of death reported as hemorrhage for 2 patients and as intestinal perforation, pulmonary embolism, dyspnea, endocarditis, and unknown for 1 patient each. Two of these 7 events reported as cause of death were considered to be related to alectinib, intestinal perforation and one case of hemorrhage. Additional details obtained from the Applicant's narrative summaries for each of these 7 patients follow.

Intestinal perforation

Death due to intestinal perforation occurred in a 69 year old woman with a history of diverticulitis. Her concomitant medications included dexamethasone. On Study Day 47, she was hospitalized for asthenia and "gluco-metabolic failure" and was diagnosed that same day with Grade 4 intestinal perforation. Blood culture results reported on Day 48 were positive for *Staphylococcus aureus* and *Escherichia coli*, and she was treated with ciprofloxacin, vancomycin, and metronidazole. Alectinib was held starting Day 48 due to AE of intestinal perforation. On Day 54, a CT scan confirmed intestinal perforation with perforation of a diverticulum; the patient died the same day.

Hemorrhage

The case of hemorrhage reported as cause of death and considered by investigator as related to alectinib involved a 47 year old man diagnosed with hemorrhage on Study Day 56 after presenting with right buttock pain, lightheadedness, and seizure. He was on anticoagulant therapy with enoxaparin due to prior history of deep vein thrombosis and pulmonary embolism. The diagnosis of hemorrhage was made based on his presenting symptoms, along with a hemoglobin value of 7.3 g/dL on Day 56, later declining to 4.1 g/dL. Investigators suspected retroperitoneal hemorrhage based on a finding of intussusception of the jejunum reported on a CT scan done a week before presentation, but no additional imaging appears to have been done for evaluation of suspected hemorrhage. Later that evening the patient died; no autopsy was performed.

The other patient with death due to hemorrhage was a 76 year old female. Concomitant medications included the anticoagulant tinzaparin. She was hospitalized on Study Day 35 for right hip pain, and an ultrasound of the hip done on Day 26 showed a tear of the medium gluteal ligament (Grade 3 ligament rupture) and a wrenching of the femur with major hematoma involving the buttocks and right thigh. That same day, hemoglobin decreased from prior value of 9.6 g/dL (on Day 30) to 5.7 g/dL, and she was transfused red blood cells. A chest

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x-ray reportedly showed disease progression in the left lung. Alectinib was discontinued on Day 35, reportedly due to the AE of ligament rupture. On Day 37, she developed hypoxia and per the narrative “went into a coma due to disease progression”. She died that same day, with cause of death reported as serious hemorrhage.

Pulmonary embolism

One day prior to starting treatment with alectinib, a 51 year old male with a history of pulmonary thromboembolism had imaging which revealed evidence of persistent intraluminal repletion defects the segmental and subsegmental branches of the right lower lobe pulmonary artery consistent with pulmonary embolism, associated with triangular peripheral opacities in the right lower lobe, related to small lung infarctions. Concomitant medications included enoxaparin, which, according to the narrative, he had started taking one day prior to starting treatment with alectinib. He presented with dizziness and dyspnea on Study Day 16, followed by headache with generalized weakness. His oxygen saturation was 76%, a CT angiography revealed worsening of pulmonary embolism. Troponin was elevated at 0.6 micrograms/L (normal value 0.01 micrograms/L) 3 hours after the event and at 1.39 at 6 hours after the event. On Study Day 17, he was reportedly doing well (with oxygen saturation 97%) until later in the day when his oxygen saturation was recorded as 34.5% with an arterial partial pressure of oxygen measured at 24 mmHg (normal range 69-116 mmHg). He was treated with aspirin, oxygen, nitroglycerin, and blood transfusion but died that same day.

Dyspnea

There is limited information available for the 70 year old female whose cause of death was reported as dyspnea. She was hospitalized on Study Day 26 for Grade 3 dyspnea and was treated with oxygen. Alectinib was discontinued that same day due to AE of dyspnea. She died 3 days later (Day 29), reportedly due to “worsening of dyspnea”. There was no information provided regarding imaging studies done at the time of the event or regarding autopsy. The investigator considered the event of dyspnea to be unrelated to alectinib, but no other possible cause of the event was specified.

Endocarditis

A 42 year old man started treatment with alectinib on [REDACTED] (b) (6) on Study NP28673. Imaging done on Study Day 345 showed findings consistent with PD, including new lesions in hepatic hilar lymph nodes. That same day he entered Part 3 of the study, which allowed for continuation of study treatment with alectinib beyond progression. He was hospitalized on Day 380 with dyspnea, and an echocardiogram showed findings of endocarditis. Endocarditis was treated with vancomycin and meropenem. There was no change in alectinib administration due to the event of endocarditis. He died a week later (Day 387); no autopsy was performed.

Unknown

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The cause of death was reported as unknown for a 48 year old man who started treatment with alectinib on [REDACTED] (b) (6). His sites of disease for NSCLC included brain metastases. Listing of past cancer treatments included “palliative radiotherapy” to left temporal, right frontal, and occipital areas in mid-2013, and reported medical history included “two episodes of stereotactic radiosurgery” with specific dates not noted. Target lesions at the time of screening included a right frontal brain metastasis. Imaging on Study Day 77 showed PD with a new lesion in the right occipital region, but treatment with alectinib was continued. On Day 208, at which time he was still taking alectinib, he presented with left hemiparesis. A CT scan of the head showed progressive vasogenic edema associated with a 5.6 mm hyperdense subcortical lesion in the medial right occipital lobe, and IV dexamethasone was started. The following day (day 209), he had a seizure and was started on anti-seizure medication. On Day 210, findings on brain MRI included acute brain infarction involving the high right frontal parietal cortex at the central sulcus; alectinib administration was temporarily interrupted that same day but was restarted prior to discharge (date not listed). He was transferred to a rehabilitation center on an unknown date and was discharged from there on Day 227. Follow-up imaging done Day 230 at an outpatient visit with his medical oncologist revealed PD, alectinib was stopped. At that visit, Grade 2 headache and Grade upper respiratory infection were reported, and he started treatment with dexamethasone for headache and doxycycline for upper respiratory infection. On Day 232, a “coroner” called to inform the study site that the patient had died; no autopsy was performed.

Reviewer Comment: There were a relatively small number of deaths (7 deaths in 253 patients, 2.8%) attributed to causes other than progressive disease across Studies NP28761 and NP28673. Review of the details of these deaths does not raise a safety concern.

8.4.2. Serious Adverse Events

Among 253 patients, 49 patients (19%) experienced 68 SAEs. The incidence rates of specific SAEs (by preferred term) were low. The table below lists SAEs by preferred term that occurred in >1 patient. Potential drug-relatedness of these SAEs will not be discussed since these reports are from single arm trials.

Table 30: Serious Adverse Events Occurring in >1 Patient (n=253) (Reviewer Table)

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Preferred Term	n	%
Dyspnea	3	1.2
Pulmonary embolism	3	1.2
Hyperbilirubinemia	3	1.2
AST increased	2	0.8
ALT increased	2	0.8
Hemorrhage	2	0.8
Influenza	2	0.8

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

The pre-specified safety withdrawal criteria for Study NP28761 and Study NP28673 were reasonable; see study designs in Sections 6.1.1 and 6.1.2 of this review. A total of 15 patients (6%) discontinued study drug to due to AEs. The following table lists AEs by preferred term leading to discontinuation of alectinib.

Table 31: Adverse Events Leading to Discontinuation of Alectinib (n=253) (Reviewer Table)

Preferred Term	n	%
ALT increased	4	1.6
Hyperbilirubinemia*	4	1.6
AST increased	3	1.2
Drug-induced liver injury	1	0.4
Blood creatinine increased	1	0.4
INR increased	1	0.4
Hemorrhage	1	0.4
Dyspnea	1	0.4
Interstitial lung disease	1	0.4
Intestinal perforation	1	0.4
Pneumonia	1	0.4
Ligament rupture	1	0.4

*Includes preferred term "blood bilirubin increased"

8.4.4. Significant Adverse Events

For a listing of treatment-emergent AEs (TEAEs), including a listing of Grade ≥ 3 TEAEs, see Section 8.4.5 of this review. The following tables list AEs by preferred term that led to dose reduction or dose interruption of alectinib in >1% of patients. Dose reductions due to AEs occurred in 29 patients (12%), and at the time of the data cut-off for the 90-Day Safety Update (27 Apr 2015), the median time to dose reduction was 48 days (range 2-469 days).

Table 32: Adverse Events Leading to Dose Reduction of Alectinib in >1% of Patients (n=253) (Reviewer Table)

Preferred Term	n	%
Hyperbilirubinemia*	6	2.4
Creatine phosphokinase increased	5	2.0
AST increased	4	1.6
Edema peripheral	3	1.2

*Includes preferred term “blood bilirubin increased”

Dose interruption due to AEs occurred in 68 patients (27%). At the time of the data cut-off for the 90-Day Safety Update (27 Apr 2015), the median time to dose interruption was 53 days (range 1-462 days), and the median duration of study drug interruption was 7 days (range 1-33 days).

Table 33: Adverse Events Leading to Dose Interruption of Alectinib in >1% of Patients (n=253) (Reviewer Table)

Preferred Term	n	%
Hyperbilirubinemia*	11	4.3
ALT increased	8	3.2
Creatine phosphokinase increased	6	2.4
Nausea	6	2.4
Vomiting	6	2.4
Diarrhea	4	1.6
AST increased	3	1.2
Creatinine increased	3	1.2
Pyrexia	3	1.2

*Includes preferred terms “blood bilirubin increased” and “bilirubin conjugated increased”

Selected AEs were presented by the Applicant as “Other Significant Adverse Events” (see Section 8.3.2 for additional details). Many of these are addressed in other sections of this review, as noted in the following list. Those not addressed in other sections of this review will be discussed here. Other significant AEs (with reference to relevant section of this review) per the Applicant were: hepatocellular or cholestatic AEs and abnormal liver function tests (Section 8.4.6), bradycardia (Section 8.4.7), QT interval prolongation (Section 8.4.9), muscular AEs and CPK elevations (Section 8.5.1), interstitial lung disease (Section 8.5.2), vision disorders (Section 8.5.3, gastrointestinal AEs, skin disorders, hematologic abnormalities, abnormal kidney function AEs, and edema.

Gastrointestinal AEs

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Gastrointestinal AEs were reported in 153 of 253 patients (61%). The majority of these events were Grade 1 or 2 in severity, with Grade ≥ 3 events reported in 9 patients (4%). The most commonly reported gastrointestinal AEs (all grades, occurring in $>10\%$ of patients) by preferred term were: constipation (34%), nausea (18%), diarrhea (16%), and vomiting (12%). Grade ≥ 3 AEs (occurring in 1 patient each unless otherwise noted) were constipation (n=3), upper abdominal pain (n=2), vomiting, intestinal perforation, intestinal obstruction, and rectal hemorrhage; these included one Grade 5 event (intestinal perforation).

Skin disorders

Skin disorders were reported in 96 of 253 patients (38%), and the most commonly reported events by preferred term were rash (12%) and photosensitivity reaction (10%). There was one (0.4%) Grade 3 AE reported (rash), with the remainder of events Grade 1 or 2 in severity. For labeling purposes, the Applicant proposed the use of a composite term for "rash", consisting of rash, rash maculopapular, dermatitis acneiform, erythema, rash generalized, rash papular, rash pruritic, and rash macular; using this composite term, AE of rash occurred in 18% of patients.

Reviewer Comment: The composite term "rash", as defined by the Applicant, is reasonable.

In vitro photosafety testing of alectinib suggested a potential risk of phototoxicity, and photosensitivity reactions have been reported with other ALK inhibitors. Therefore, photosensitivity was identified by the Applicant as an important identified risk for alectinib. Among the 253 patients included in the ISS, photosensitivity reaction was reported as an AE for 25 patients (10%). There was one (0.4%) Grade 2 event reported, with the remainder of photosensitivity reaction events Grade 1 in severity. Recommendations to avoid prolonged sun exposure and use broad spectrum sunscreen and lip balm due to the risk of photosensitivity with alectinib treatment were not included in the original versions of the protocols for Studies NP28761 and NP28673 but were added in later amendments (Version 6.0 for NP28761 and Version 3.0 for NP28673). An information request was sent to the Applicant requesting the incidence of photosensitivity reactions in each study during the time periods before and after implementation of these protocol amendments. For NP28761, all patients receiving treatment prior to implementation of the amendment were in the phase I portion of the study, and the incidence of photosensitivity was 9.8%. For patients in the phase I portion of NP28761 receiving treatment after implementation of the amendment, photosensitivity reactions were reported in 4.9% of patients. All patients in the phase II portion of Study NP28761 and all patients in Study NP28673 received treatment with alectinib after implementation of the relevant amendments, and photosensitivity reactions were reported in 10.3% and 10.1% of patients, respectively.

Reviewer Comment: The incidence of photosensitivity reactions did not decrease after implementation of protocol amendments including recommendations for patients to avoid sun exposure and use broad spectrum sunscreen. Data on patient avoidance of sun exposure and

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use of sunscreen were not routinely collected as part of these studies, so no conclusions can be drawn regarding the effectiveness, or lack thereof, of these measures in reducing the incidence of photosensitivity reactions.

Hematologic abnormalities

Hematologic abnormalities were reported in 53 of 253 patients (21%). Abnormalities by preferred term occurring in >1 patient were anemia (14%), neutropenia (3%), leukopenia (3%), lymphopenia (1%), neutrophil count decreased (1%), white blood cell decreased (1%), and hemoglobin decreased (1%). The majority of these events were Grade 1 or 2 in severity, with Grade ≥ 3 event reported in 6 patients (2%). Grade ≥ 3 AEs were anemia (n=4), neutropenia (n=1) and lymphopenia (n=1). For details regarding anemia as assessed by laboratory shift data, see Section 8.4.6 of this review.

Abnormal kidney function AEs

Abnormal kidney function AEs were reported in 48 of 253 patients (19%). AEs reported in >1 patient were blood creatinine increased (6%), pollakuria (4%), nocturia (3%), hematuria (2%), dysuria (2%), proteinuria (1%), urinary retention (1%), azotemia (1%), and urinary incontinence (1%). The majority of these events were Grade 1 or 2 in severity, with Grade ≥ 3 event reported in only 1 patient (0.4%); the Grade ≥ 3 AE was blood creatinine increased. For details regarding increases in creatinine as assessed by laboratory shift data, see Section 8.4.6 of this review.

Edema

For purposes of labeling, the Applicant proposed using a composite term for edema, consisting of the preferred terms edema peripheral, edema, generalized edema, eyelid edema, and periorbital edema. Based on this composite term, edema (all grades) was reported in 30% of patients, including Grade 3-4 edema in 2 patients (0.8%). An AE of weight increased was reported in 27 patients (11%), but there is no information available to determine how many, if any, of these AEs were related to fluid retention. No AEs using the preferred terms of pulmonary edema or congestive heart failure were reported.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The most common TEAEs ($\geq 25\%$) reported for alectinib administered at a dose of 600 mg BID were fatigue (including the preferred terms fatigue and asthenia), constipation, edema (composite term defined by Applicant), and myalgia (composite term defined by Applicant). For definitions of composite terms, see footnotes for the below table; the following table lists TEAEs occurring in $\geq 10\%$ (all Grades) or $\geq 2\%$ (Grade 3-4) of patients.

Reviewer Comment: The Applicant reported fatigue and asthenia separately, while the reviewer determined that it would be more appropriate to report these as a composite term "fatigue".

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Table 34: Treatment-Emergent Adverse Events Occurring in ≥10% (All Grades) or ≥2% (Grade 3-4) of Patients (n=253) (Reviewer Table)

Preferred Term or Composite Term	All Grades (%)	Grade 3-4 (%)
Fatigue ¹	41	1.2
Constipation	34	0
Edema ²	30	0.8
Myalgia ³	29	1.2
Cough	19	0
Rash ⁴	18	0
Nausea	18	0.4
Headache	17	1.2
Diarrhea	16	0.8
Dyspnea	16	3.6
Vomiting	12	0.4
Back pain	12	0
Weight increased	11	0
Vision disorder events ⁵	10	0

¹Includes fatigue and asthenia

²Includes edema peripheral, edema, generalized edema, eyelid edema, periorbital edema

³Includes myalgia and musculoskeletal pain

⁴Includes rash, rash maculopapular, dermatitis acneiform, erythema, rash generalized, rash popular, rash pruritic, rash macular

⁵Includes blurred vision, visual impairment, vitreous floaters, reduced visual acuity, asthenopia, diplopia

It is appropriate to include all of these TEAEs in the Adverse Reactions section of the prescribing information for alectinib, since these data are derived from single arm trials.

8.4.6. Laboratory Findings

The following table lists treatment-emergent laboratory abnormalities, based on laboratory shift tables, occurring in >20% of patients treated with alectinib 600 mg BID. Laboratory shift results were available for 250 of the 253 patients included in the ISS, with the exception of CPK results, which were available for 218 patients.

Table 35: Laboratory Abnormalities Occurring in >20% of Patients (n=250) (Reviewer Table)

Parameter	All Grades (%)	Grade 3-4 (%)
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Anemia	56	2.0
Increased AST	51	3.6
Increased creatine phosphokinase ¹	43	4.6
Hyperbilirubinemia	40	2.8
Increased ALT	34	4.8
Increased creatinine	34 ²	1.2

¹n=218 with baseline CPK values missing for 91 of these patients

²See paragraph following this table for details regarding estimation of the incidence of increased creatinine

For increased creatinine, NCI-CTCAE v4.03 defines Grade 1 as “>1-1.5x baseline; >1-1.5x ULN”. Using these criteria, the incidence of increased creatinine among 250 patients with laboratory shift data available was 95%. Due to the inclusion of patients with creatinine >1-1.5x baseline, this group may include a significant number of patients whose creatinine is still within normal limits for the laboratory test. For the estimation of increased creatinine used in the above table, creatinine above the ULN was used to define all Grade increased creatinine, as this definition is more clinically relevant. The reviewer used JMP to estimate a head count incidence of creatinine above the ULN based on the datasets provided for the ISS; this yielded an incidence of 29% (74 of 253 patients). These results do not account for baseline creatinine values. Only 7 patients had creatinine greater than ULN at baseline based on laboratory shift tables.

Reviewer Comment: The Sponsor has been asked to perform a similar assessment to determine the percentage of patients with creatinine greater than ULN for use in labeling.

Among patients with elevations of liver function tests, no Hy’s law cases were identified. Additional analyses were conducted by the reviewer for liver function test abnormalities (increased AST, increased ALT, and hyperbilirubinemia). Narratives, including relevant laboratory data, were reviewed for the 18 patients (7%) who experienced Grade ≥ 3 elevation of AST, ALT, and/or bilirubin based on laboratory test results. All but one event was Grade 3. In one patient, alectinib dosing was interrupted 3 days after an initial event of Grade 3 AST and ALT elevation; toxicity progressed to Grade 4 a few days later, leading to permanent discontinuation of alectinib.

Overall, 8 of these 18 patients (44%; 8 of 253 [3.2%]) with Grade ≥ 3 elevation of AST, ALT, and/or bilirubin discontinued treatment with alectinib due to the relevant AE. Three patients discontinued treatment with alectinib close to the occurrence of AE of Grade ≥ 3 elevation, but reason for discontinuation was listed as increased INR and PD for 1 patient and PD for the other 2 patients. Of the 8 patients who discontinued treatment due to Grade ≥ 3 elevation of AST, ALT, and/or bilirubin, 4 were reported as discontinued due to hyperbilirubinemia and 4 were reported as discontinued due to elevation of AST and/or ALT; this included 1 patient with hyperbilirubinemia with 2nd episode of hyperbilirubinemia occurring after dose reduction for

previous Grade 3 hyperbilirubinemia. Two of these patients, both with elevations of AST/ALT, had liver biopsy done as part of the evaluation of elevated liver function tests, and in both cases findings were suggestive of drug-induced liver injury.

Eight of the 18 patients had alectinib dose reduced for Grade ≥ 3 elevation of AST, ALT, and/or bilirubin. For 6 of these patients, the dose was reduced following first occurrence of the event; for 2 patients, dose reduction did not occur until 2nd occurrence of Grade ≥ 3 elevation of AST, ALT, and/or bilirubin (following dose interruption). Six of these 8 patients had no recurrence of Grade ≥ 3 elevation of AST, ALT, and/or bilirubin following dose reduction of alectinib. Two patients experienced a 2nd episode of hyperbilirubinemia following initial dose reduction; one patient had alectinib discontinued (patient discussed in the previous paragraph), while the other had alectinib dose reduced a 2nd time with no additional recurrence of Grade ≥ 3 elevation of AST, ALT, and/or bilirubin.

8.4.7. Vital Signs

Both systolic and diastolic blood pressure showed a slight median decrease from baseline, returning to baseline at follow-up. For patients in the phase II portion of Study NP28761, median decreases in systolic and diastolic blood pressure were 3 mmHg and 6 mmHg, respectively, after 4 weeks of treatment, and 2 patients (2%) reported AEs of orthostatic hypotension and 1 patient (1%) reported an AE of hypotension. For patients in the phase II portion of Study NP28673, median decreases in systolic and diastolic blood pressure were 4 mmHg and 8 mmHg, respectively, after 6 weeks of treatment, and no AE of hypotension was reported.

Bradycardia is considered a class effect of ALK inhibitors and was identified by the Applicant as an important identified risk for alectinib. Alectinib treatment resulted in a decrease from baseline in mean heart rate of approximately 11 to 13 beats per minute at Week 2, and heart rate was stable thereafter and maintained throughout treatment with alectinib. Of 221 patients with ECG analyzed as part of Studies NP28761 and NP28673, 20% had heart rates < 50 beats per minute. AEs of bradycardia (including the preferred terms bradycardia and sinus bradycardia) were reported in 19 of 253 patients (7.5%). All events were of Grade 1 or 2 in severity. The event of bradycardia were associated with AEs of clinical relevance in 2 patients; one patient, who was receiving concomitant therapy with a beta-blocker and a benzodiazepine, experienced AEs of PR prolongation and AV block (both Grade 1), while another patient experienced AE of dizziness (Grade 1). Alectinib was dose reduced in 1 patient for Grade 2 bradycardia, and alectinib dosing was interrupted in 1 patient for Grade 1 sinus bradycardia.

8.4.8. Electrocardiograms (ECGs)

For detailed information on ECG findings from this study, refer to the review by the FDA

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Interdisciplinary Review Team for QT studies (QT-IRT), which was consulted for this NDA. The QT-IRT concluded that neither PR nor QRS was affected to any clinically significant extent; Findings related to QT interval are discussed in Section 8.4.9 of this review. The QT-IRT noted that alecensa treatment resulted in a concentration-dependent decrease from baseline in mean heart rate (HR) of approximately >10 beats per minute (bpm) at the steady state. The QT-IRT noted that “the bradycardia is concerning” and that the Investigator’s Brochure for alecensa did not contain a detailed explanation for this finding and implied that bradycardia occurring in the clinical development program should be reviewed as a safety issue.

The observed decrease in mean heart rate resulted in a low incidence of treatment-related AEs of bradycardia/sinus bradycardia (7.5% based on 90-Day Safety Update Report). All events were non-serious and of Grade 1 or 2 in severity. None of the events of bradycardia/sinus bradycardia were associated with AEs of clinical relevance, except for one case of sinus bradycardia associated with dizziness (both Grade 1). Bradycardia is one of the submission-specific safety issues chosen for more detailed assessment in this review; see Section 8.4.7 for additional discussion of this issue.

8.4.9. QT

The ability of alecensa to prolong the QT interval was assessed in 221 patients administered alecensa 600 mg BID in clinical studies. Alecensa did not prolong the QTc interval to any clinically relevant extent. Two patients had a maximum post-baseline QTcF value of >500 msec or a maximum QTcF change from baseline of >60 msec.

The QT-IRT was consulted; please see their review for full details. The QT-IRT reviewed and conducted data analyses for only Study NP28761. All of the 47 patients in the phase I portion of the study and 84 of the 87 patients in the phase II portion were included in the ECG population. The QT-IRT concluded that alecensa did not cause a large, clinically relevant change in QTcF interval in Study NP28761 and stated that no clear dose-dependent QTc effect was observed. The QT-IRT noted no evidence of an exposure-dependent increase in Δ QTcF.

The study report for Study NP28673 and the ECG report for the pooled analysis (106041) were not noticed until the time of secondary review. Due to the short timeline and adequate information from Study NP28761, only report reviews were conducted for NP28673 and report 106041. Based on the report reviews, the QT-IRT considered the cardiac safety findings from NP28673 and the pooled ECG analysis presented in 106041 consistent with the results observed in NP28761 and noted no clinically relevant effect on QTc at the therapeutic exposure.

The following is the QT-IRT’s proposed labeling language for the Cardiac Electrophysiology heading under Section 12.2 Pharmacodynamics:

“Serial triplicate ECGs were collected following a single dose and at steady-state to

evaluate the effect of alectinib on the QT interval in the two clinical trials. A total of 221 patients treated with ALECENSA 600 mg BID were included in the analysis. ALECENSA 600 mg BID did not cause a clinically relevant effect on QTcF.

“Alectinib treatment resulted in a concentration-dependent decrease from baseline in mean HR of approximately 11 to 13 bpm at Week 2, which was stable thereafter and was maintained throughout treatment and was generally asymptomatic.”

8.4.10. Immunogenicity

This subsection is not relevant to this review, as alectinib is not associated with a concern for immunogenicity.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Muscular AEs and Creatine Phosphokinase Elevations

The safety issue of muscular AEs and CPK elevations was assessed in detail by the Applicant due to the incidence of these events observed in clinical studies of alectinib. Muscular AEs and/or CPK elevations were reported in 142 of 253 patients (56%), with the most commonly reported AEs by preferred term myalgia (24%), back pain (12%), and blood CPK increased (12%). For labeling purposes, the Applicant proposed the use of a composite term for “myalgia”, consisting of the preferred terms myalgia and musculoskeletal pain. Using this composite term, myalgia occurred in 29% of patients, with Grade ≥ 3 myalgia reported in 3 patients (1.2%).

Reviewer Comment: The composite term “vision disorder”, as defined by the Applicant, is reasonable.

It is important to note that CPK was included as part of routine clinical testing in Study NP28761 from the start of the study but was not added as part of routine clinical testing in Study NP28673 until implementation of the amendment for Protocol Version 4 (dated 19 Nov 2013). Therefore, CPK values are not available for every patient with reported AE of myalgia. For the 3 patients who experienced Grade 3 myalgia, only one had CPK results close to the time of the event (patient included in Table 36 and

Table 37); one had no CPK data available, and one had only one CPK result available at a timepoint (Week 36) long after the AE of Grade 3 myalgia (Day 29). The Applicant states that

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no event of myalgia was associated with CPK values exceeding 10,000 U/L or renal failure, and thus there were no cases meeting the definition of rhabdomyolysis as per criteria of the National Lipid Association (NLA) guidance²².

Additional analyses were conducted by the reviewer for CPK elevations. Based on laboratory shift data, CPK elevations occurred in 43% of 218 patients with CPK laboratory data available; baseline CPK values were missing for 91 of these patients. Grade 3 elevation of CPK occurred in 10 of these 218 patients (4.6%); there were no cases of Grade 4 CPK elevation. Of the 10 patients experiencing Grade 3 CPK elevation, concomitant AE of myalgia was reported in 3 patients. At the reviewer’s request, ad hoc narratives containing details related to the AE of elevated CPK were provided by the Applicant for these 3 patients. Table 36 provides information on timing of Grade 3 CPK elevation in these patients and actions taken.

Table 36: Grade 3 Creatine Phosphokinase Elevation Occurring in Conjunction with Myalgia (Reviewer Table)

	Day of treatment Grade 3 CPK occurred	# of days until resolution to Grade ≤1 documented	# of days alectinib was held	Dose used when treatment restarted	Grade of myalgia
Case 1	15	7	7	450 mg BID	1
Case 2	15	7	6	600 mg BID	1
Case 3	15	10	16	450 mg BID	3

Note: All patients were taking alectinib 600 mg BID at the time of the event

For all 3 events, alectinib was held for Grade 3 CPK elevation until toxicity had resolved to Grade ≤1 and was then restarted. In 2 of 3 cases, alectinib was restarted at a reduced dose of 450 mg BID, and for these 2 patients no occurrence of CPK elevation Grade >1 was recorded after restarting alectinib. For the patient who restarted treatment at the initial dose of 600 mg BID, CPK elevation of Grade 2 was documented on two separate occasions (Day 57 and Day 204); no adjustments to alectinib dosing were made for these findings, and CPK elevation resolved to Grade ≤1 by the time of next assessment (Day 78 and Day 225, respectively). None of these patients had an AE of renal failure occurring in conjunction with Grade 3 CPK elevation.

Table 37: Time Course for Concomitant Adverse Event of Myalgia with Grade 3 Creatine Phosphokinase Elevation (Reviewer Table)

	Grade 3 CPK	Resolution to Grade ≤1	Alectinib restarted	Myalgia day of onset	Myalgia day of resolution	CPK values at other relevant times
Case 1	D15	D22	D22	D22	D87	Grade 1 D22, normal from D43 to D92
Case 2	D15	D22	D22	D11 D371 (intermittent)	D99 N/A	Normal D8, Grade 2 D57, otherwise Grade 1 from D22 to D99 Normal D372 to D477 except Grade 1 twice (D435, D456)
Case 3	D15	D25	D31	D3 D32	D23 D32*	Normal D1, Grade 3 D17 & D18, Grade 2 D20 & D21 Normal D29 and D35

Reviewer Comment: While it is possible that these AEs of myalgia were related to alectinib, it is not possible to establish a clear association between the occurrence of myalgia and Grade 3 elevations of CPK.

The reviewer also requested the Applicant provide a listing of CPK and creatinine values throughout treatment and information on any dose modifications made as a result of CPK elevation for the 10 patients experiencing Grade 3 elevations of CPK. All 10 patients had at least Grade 1 creatinine increase based on CTCAE v4.03 criteria; however, only 2 of 10 patients ever had creatinine above the laboratory ULN. One patient experienced Grade 1 increased creatinine (with creatinine above ULN), with the initial event occurring in conjunction with Grade 3 CPK elevation; alectinib dose was reduced. This patient's creatinine decreased to below ULN within a week, but similar Grade 1 elevations (with creatinine above ULN) occurred in this patient later in the study, with CPK elevation Grade ≤3. One patient had an event of Grade 2 increased creatinine (with creatinine above ULN) in conjunction with Grade 3 CPK

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elevation (study day 196 for patient). There was no interruption or reduction of alectinib dose, and both improved to Grade 1 by next test date (study day 224); a later episode of Grade 2 increased creatinine (with value above ULN) occurred in conjunction with Grade 2 CPK elevation (study day 252) but again improved without dose modification (to Grade 1 and Grade 0, respectively, on study day 280). The closest date with a musculoskeletal AE reported for this patient was study day 224 (musculoskeletal chest pain); no musculoskeletal AE was reported study day 196 or day 252.

Among the 10 patients experiencing Grade 3 CPK elevation, 5 patients had alectinib dose reduced due to AE of elevated CPK. For 3 patients, alectinib dosing was interrupted then restarted at the initial dose, with no recurrence of Grade 3 CPK elevation. By review of the data provided by the Applicant, it appears one patient was treated through Grade 3 CPK elevation (discussed in preceding paragraph); this patient did not experience a 2nd occurrence of Grade ≥ 3 CPK elevation. One patient had alectinib dosing interrupted for Grade 3 CPK elevation but never restarted treatment due to finding of PD. No patient discontinued treatment with alectinib due to CPK elevation.

In the supportive study, AF-001JP, conducted in Japan, AEs included in the rhabdomyolysis / myopathy Standardized MedDRA Query (SMQ) occurred in 35 of 58 patients (60%) treated with the RP2D for that study, alectinib 300 mg BID. The most common preferred terms for these events were blood creatinine increased (29%), blood CPK increased (28%), and myalgia (21%). The reported AEs included in this SMQ were Grade 1-2, except for Grade ≥ 3 elevations of CPK reported in 5 patients (9%). The Applicant states that no cases of rhabdomyolysis were reported. Alectinib dosing was interrupted in 3 patients (5%) for increased CPK and in 2 patients (3%) for increased creatinine, but none of the AEs reported under this SMQ led to dose reduction or withdrawal of alectinib.

8.5.2. Interstitial Lung Disease

Interstitial lung disease (ILD) is considered a class effect of tyrosine kinase inhibitors, including ALK inhibitors and was identified by the Applicant as an important identified risk for alectinib. One case of ILD was reported among 253 patients (0.4%) included in the ISS. This case of ILD was Grade 3, reported as serious, and assessed by the investigator as related to alectinib. Alectinib was permanently discontinued; the AE of ILD was reported as still ongoing at the time of data cut-off.

The CRFs for all 20 patients with respiratory AEs encompassing the following preferred terms were examined by the reviewer to assess for possible missed cases of ILD: pneumonia (n=11), pneumonia bacterial (n=1), lung infection (n=3), lower respiratory tract infection (n=1), and respiratory tract infection (n=4). Based on the available information, none of these events were suspicious for ILD or pneumonitis. Two of the 20 patients did receive steroid as part of their treatment for respiratory AE. In one of these patients, with AE reported as pneumonia,

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laboratory findings of leukocytosis with elevated neutrophil count and radiographic findings of lung consolidation on chest x-ray along supported a diagnosis of pneumonia rather than pneumonitis; CT scan was done and showed findings consistent with bronchial obstruction related to PD. The other patient treated with steroids had an AE reported as lung infection and received only 5 days of treatment with prednisolone, which is more consistent with steroid use for the treatment of a suspected respiratory infection in a patient with underlying lung disease (i.e., chronic obstructive pulmonary disease exacerbation, rather than treatment of suspected ILD or pneumonitis.

8.5.3. Vision Disorders

A significant number of vision disorder AEs have been reported in studies of other ALK inhibitors. Ophthalmologic examination was not included as a routine study evaluation for either study, and baseline ophthalmologic examinations were not required. Vision disorder AE of any type was reported in 43 of 253 patients (17%), with the most common reported AEs by preferred term vision blurred (4%), vitreous floaters (2%), and visual impairment (2%). One (0.4%) Grade 3 vision disorder AE was reported (retinal detachment, assessed by investigator as unrelated to treatment with alectinib), while the remainder of events were Grade 1 or 2 in severity. For labeling purposes, the Applicant proposed the use of a composite term for “vision disorder”, consisting of blurred vision, visual impairment, vitreous floaters, reduced visual acuity, asthenopia, and diplopia; using this composite term, AE of vision disorder occurred in 10% of patients.

Reviewer Comment: The composite term “vision disorder”, as defined by the Applicant, is reasonable. The incidence of specific visual disorders by preferred term are relatively low, with the most common AE, vision blurred, occurring in 4% of patients. In addition, all vision disorder events were Grade 1 or 2 in severity, with the exception of one Grade 3 event which was most likely not related to treatment with alectinib.

8.6. Specific Safety Studies/Clinical Trials

This subsection is not applicable to this review, as no separate studies have been conducted to evaluate specific safety concerns.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

For full details, please see Pharmacology / Toxicology review. Carcinogenicity studies with alectinib have not been conducted. Alectinib was not mutagenic in the bacterial reverse mutation (Ames) assay, but a rat bone marrow micronucleus test for mutagenicity was positive

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with an increased number of micronuclei. The mechanism of micronucleus induction was abnormal chromosome segregation and not a clastogenic effect on chromosomes.

Across the two pivotal clinical trials, there were no deaths, serious AEs, or discontinuations due to AE related to malignancy other than underlying NSCLC.

8.7.2. Human Reproduction and Pregnancy

For full details, please see Pharmacology / Toxicology review. Based on its mechanism of action, alectinib may cause fetal harm when administered to pregnant women. In non-clinical studies, events including embryonic and fetal death, abortion, and visceral abnormalities (rat and rabbit) have been reported. There is no clinical experience with alectinib in pregnant or lactating women, as these populations were excluded from participation in the alectinib clinical trial program. Patients were required to use adequate methods of contraception during treatment and for at least 3 months after the last dose of alectinib. No pregnancies were reported in the clinical studies included in the ISS. There is no data on the presence of alectinib or its metabolites in human milk, the effects of alectinib on the breast-fed infant, or its effects on milk production.

No animal studies have been performed to specifically evaluate the effect of alectinib on fertility. Effects on male reproductive organs were observed in general toxicology studies conducted in rats and monkeys. In rats, glandular atrophy was reported in the prostate and seminal vesicles at doses resulting in exposures approximately 2.4 times the estimated area under the curve (AUC) with alectinib 600 mg BID. In monkeys interstitial fibrosis of the testis was observed at approximately 0.2 times the estimated AUC with alectinib 600 mg BID.

A consult was obtained from the Division of Pediatric and Maternal Health (DPMH); for full details, see DPMH Memorandum by Dr. Suchitra Balakrishnan. Recommendations were that pregnant women considering use of alectinib should be advised of the potential risk to a fetus and females of reproductive potential should be advised to use effective contraception during treatment with alectinib and for 1 week following the final dose. Based on genotoxicity findings, males with female partners of reproductive potential should be advised to use condoms during treatment with alectinib and for 3 months following the final dose. Breastfeeding is not recommended during treatment with alectinib and for 1 week after the final dose.

8.7.3. Pediatrics and Assessment of Effects on Growth

For full details, please see Pharmacology / Toxicology review. The subsection has limited relevance for this NDA application, as NSCLC is extremely rare in the pediatric population.

8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

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No experience with overdose relevant to the recommended dose of alectinib is available. There were no cases of study drug overdose in the two pivotal studies, NP28761 and NP28673. In the supportive study, AF-001JP, 5 cases of study drug overdose (i.e., doses >300 mg BID) were reported, with the highest reported dose 450 mg BID. There were no cases of AEs associated with any of these cases of overdose. There is no specific antidote for overdose with alectinib. Alectinib and its major active metabolite M4 are > 99% bound to plasma proteins; therefore, hemodialysis is likely to be ineffective in the treatment for overdose.

A Controlled Substance Staff (CSS) consultation was not obtained, as there are no concerns regarding the potential for abuse, withdrawal, or rebound with alectinib. On the basis of its pharmacological properties, the risk of abuse or misuse of alectinib is low.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

Alectinib 600 mg BID has not been approved for use anywhere in the world; therefore, no post-marketing data is available for this dosage. Alectinib was granted marketing approval in Japan on 4 July 2014 for the treatment of “ALK fusion gene-positive unresectable, recurrent or advanced non-small cell lung cancer”. The recommended dose in Japan is 300 mg orally BID, and it is marketed by Chugai in 20 mg and 40 mg capsules to be taken orally. Per the ISS for the current application, as of 3 Jan 2015, no regulatory actions were had been undertaken for safety reasons by either the regulatory authorities or by Chugai, the Marketing Authorization Holder in Japan, and a review of the postmarketing data by the Applicant did not reveal any new, pertinent safety information for alectinib. The most recent Development Safety Update Report (DSUR) for alectinib, covering the reporting interval from 4 Jun 2014 to 3 Jun 2015, states that post-marketing data that became available from Japan during the reporting interval did not reveal any new, pertinent safety information. During the reporting interval, no safety-related amendments were made to the Japanese label for alectinib or to Chugai’s risk management plan for alectinib based on the post-marketing data.

8.8.2. Expectations on Safety in the Postmarket Setting

The safety database does not include a sufficient number of subjects aged 65 and older to determine whether they respond differently from younger subjects. However, based on the overall safety profile of alectinib, there are no specific safety concerns regarding the use of alectinib in older patients. There are no safety concerns regarding potential differences in how the drug was administered and used in the clinical trials versus its expected use in the postmarket setting. Off-label use in patients with non-NSCLC tumors documented to have ALK rearrangement is anticipated, but there are no specific safety concerns expected from this potential off-label use.

8.9. Additional Safety Issues From Other Disciplines

There are no additional safety issues from other disciplines requiring discussion here.

8.10. Integrated Assessment of Safety

Based on evaluation of the safety database of patients who received treatment with alectinib at a dose of 600 mg BID on Studies NP28761 and NP28673, alectinib appears to have a reasonable safety profile when assessed in the context of the treatment of a life-threatening disease. There was not an excess of unexplained deaths. Fatal adverse reactions occurred in 2% of patients, and review of these cases does not identify a specific safety concern related to alectinib. The most common adverse reactions were fatigue, constipation, edema, and myalgia. Permanent discontinuation of alectinib due to adverse reactions occurred in only 5% of patients.

Safety issues (with reference to the sections of this review where each is discussed) which should be included in the Warnings and Precautions section of the USPI include hepatotoxicity (Section 8.4.6), interstitial lung disease (Section 8.5.2), bradycardia (Section 8.4.7), and severe myalgia and creatinine phosphokinase elevation (Section 8.5.1).

9 Advisory Committee Meeting and Other External Consultations

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 regarding the role of alectinib for this indication, and outside expertise was not necessary as there were no controversial issues that could benefit from an Advisory Committee discussion.

10 Labeling Recommendations

10.1. Prescribing Information

These recommendations for major changes to the clinically relevant aspects of the Applicant's proposed prescribing information are based on assessment of the label at the time this review was completed.

- INDICATIONS AND USAGE

- Remove the words “ (b) (4) ”.

Reviewer Comment: Only 1 patient (1%) in Study NP28761 and 2 patients (1%) in Study NP28673 had NSCLC that was not metastatic. (b) (4)

- Change “who have progressed on or are intolerant to crizotinib” to “who have progressed on crizotinib”.

Reviewer Comment: Among 87 patients treated in the phase II portion of Study NP28761, 2 patients (2%) stopped prior treatment with crizotinib due to a reason other than progression of disease, one due to AE of increased transaminases and one due to patient decision (“patient did not wish to continue”). On Study NP28673, there were no patients who had stopped crizotinib for reason other than progression of disease. There is not enough information available to assess efficacy in NSCLC patients who are intolerant to crizotinib.

- **DOSAGE AND ADMINISTRATION**

- Remove instructions to make up a missed dose of alectinib.

Reviewer Comment: Since alectinib and M4 have half-life of approximately 30 hours and accumulation of approximately 6-fold, there is no need to make up a missed dose of alectinib.

- Add a dose modification criterion for total bilirubin elevation greater than 3 times ULN with recommendation to temporarily withhold alectinib until recovery to baseline or to less than or equal to 1.5 times ULN, with resumption at reduced dose.

Reviewer Comment: Patients on Studies NP28761 and NP28673 had alectinib held for occurrence of Grade 3 hyperbilirubinemia (total bilirubin elevation of >3x ULN) and either discontinued treatment with alectinib (after first occurrence for most of these patients) or restarted alectinib at a reduced dose. See Section 8.4.6 of this review for additional details.

- Add dose modification criteria for Grade 3 and 4 CPK elevations. For Grade 3 CPK elevation, recommend temporarily withholding alectinib until recovery to baseline or to less than or equal to 2.5 times ULN then resuming at same dose. For Grade 4 CPK elevation, recommend temporarily withholding alectinib until recovery to baseline or to less than or equal to 2.5 times ULN then resuming at reduced dose.

Reviewer Comment: This recommendation is based on review of the safety data related to CPK elevation from Studies NP28761 and NP28673. For details, see Section 8.5.1 of this review.

- WARNINGS AND PRECAUTIONS

- Change subsection title from “(b) (4)” to “Hepatotoxicity”.

Reviewer Comment: Grade 3 and 4 liver enzyme elevations are considered potentially indicative of liver injury. In addition, two patients with liver biopsy results related to liver enzyme elevations showed findings suggestive of drug-induced liver injury (DILI). Therefore, the term hepatotoxicity is appropriate.

- Modify language related to interstitial lung disease. Applicant’s version stated, “Immediately (b) (4) ALECENSA treatment in patients diagnosed with ILD/pneumonitis and permanently discontinue ALECENSA if no other potential causes of ILD/pneumonitis have been identified.” Recommend language is: “Withhold ALECENSA and promptly investigate for ILD/pneumonitis in any patient who presents with worsening of respiratory symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough and fever). Permanently discontinue ALECENSA if ILD is confirmed.”

Reviewer Comment: This modification would make it clear that patients should not continue treatment with alectinib when presenting with symptoms suggestive of possible ILD/pneumonitis and that alectinib should be discontinued in all patients diagnosed with ILD/pneumonitis.

- Add subsection for “Severe Myalgia and Creatine Phosphokinase (CPK) Elevation”

Reviewer Comment: This recommendation is based on review of the safety data related to muscular AEs and CPK elevation from Studies NP28761 and NP28673. For details, see Section 8.5.1 of this review.

- ADVERSE REACTIONS

- Add the following adverse reactions to the Adverse Reactions table: fatigue (composite term including fatigue plus asthenia), cough, headache, dyspnea, back pain, increased weight, and vision disorder. For increased weight, the Applicant could consider including this preferred term as part of the composite term for edema.

Reviewer Comment: These adverse reactions occurred in $\geq 10\%$ of patients across Studies NP28761 and NP28673 based on information included in the 90-Day Safety Update for alectinib.

- Delete adverse reactions related to laboratory abnormalities from the Adverse Reactions table of the label (Table 3).

Reviewer Comment: Laboratory abnormalities based on data from laboratory shift tables, which are included in Table 4 of the label, provide a more accurate estimation of toxicity.

- DRUG INTERACTIONS

- Delete specific information related to drug interactions and simply state that no pharmacokinetic interactions with alectinib requiring dose adjustment have been identified.

Reviewer Comment: This information may be deleted as there are no (b) (4)

- USE IN SPECIFIC POPULATIONS

- For the “Geriatric Use” subsection, delete information on the (b) (4) aged 65 years and older and delete the following statement: “ (b) (4)

”
This subsection should consist of the following statement: “Clinical studies of ALECENSA did not include sufficient number of subjects aged 65 and older to determine whether they respond differently from younger subjects”.

Reviewer Comment: (b) (4)

- CLINICAL STUDIES

- Change the information in the “Efficacy Results” table to reflect ORR and duration of response results by IRC assessment for the ITT population (b) (4)

Reviewer Comment: Use of results from the ITT population is most appropriate for labeling purposes.

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- Add a statement noting that objective responses were observed in the CNS irrespective of prior brain radiation status.

Reviewer Comment: This information is clinically relevant.

- Delete information related to [REDACTED] (b) (4)

Reviewer Comment: [REDACTED] (b) (4)
[REDACTED] Therefore, this information is not appropriate for inclusion in the label.

- PATIENT COUNSELING INFORMATION
 - Add information related to severe myalgia / CPK elevation.

Reviewer Comment: This recommendation is based on review of the safety data related to muscular AEs and CPK elevation from Studies NP28761 and NP28673. For details, see Section 8.5.1 of this review.

- Add recommendation for providers to advise patients to use a broad spectrum sunscreen and lip balm to help protect against potential sunburn.

Reviewer Comment: This recommendation was moved from the Adverse Reactions section to the Patient Counseling Information section of the label, as the latter is the most appropriate place for this recommendation.

10.2. Patient Labeling

A patient package insert has been proposed by the applicant. Based upon initial review this appears acceptable, but assessment by the Division of Medical Policy Programs in the Office of Medical Policy is pending. There are no plans for a Medication Guide, patient package insert, or instructions for use to be developed.

10.3. Nonprescription Labeling

This subsection is not applicable for this review, as alectinib will require a prescription.

11 Risk Evaluation and Mitigation Strategies (REMS)

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Given the safety profile of this drug, there are no additional risk management strategies required beyond the recommended labeling. Therefore the subsequent subsections are not applicable for this review and have been omitted.

12 Postmarketing Requirements and Commitments

A clinical PMR is recommended to further assess efficacy and to support traditional approval. This study, entitled “A randomized, phase III study comparing alectinib with crizotinib in treatment-naïve anaplastic lymphoma kinase-positive advanced non-small cell lung cancer participants”, is already underway, and the Applicant has provided milestone dates for this PMR. The primary endpoint is PFS as assessed by investigators according to RECIST v1.1 criteria.

Clinical PMR: Conduct and submit the results of at least one multicenter, randomized clinical trial establishing the superiority of alectinib over available therapy in patients with metastatic ALK-positive NSCLC.

Milestone dates:

- Final protocol submission - March 2014
- Study / trial completion - March 2019 (end of study, once survival follow-up is complete)
- Final report submission - June 2018 (CSR based on the primary endpoint, PFS)

A clinical pharmacology PMR has also been recommended in order to determine an appropriate dose of alectinib in patients with moderate to severe hepatic impairment. The Applicant has provided milestone dates for this PMR.

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

Milestone dates:

- Final protocol submission - December 2015
- Study / trial completion - July 2017
- Final report submission – December 2017

13 Appendices

13.1. References

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13.2. Financial Disclosure

Signed financial disclosure was obtained by Sponsor from 330 out of 344 (95%) of the principal investigators and sub-investigators participating in Study NP28761 and from all 304 (100%) of those in Study NP28673. For 14 sub-investigators in NP28761 from whom a signed financial disclosure was not obtained, this was reportedly due to the fact that the sub-investigators were not available to sign the form despite 3 to 4 attempts. The Sponsor acted with due diligence to obtain financial disclosure information for these sub-investigators.

Disclosable financial interests were recorded by 4 investigators (1%) participating in Study NP28761 and for 2 investigators (0.6%) participating in Study NP28673. The only investigator reporting a disclosable financial interest and enrolling (b) (6) patient at a study site was Dr (b) (6), who enrolled (b) (6) patients to Study NP28761 (study site (b) (6)) and (b) (6) patients to Study NP28673 (study site (b) (6)). Given the small number of patients enrolled by Dr. (b) (6) to each study, data from these sites would not be expected to significantly influence the safety results of either study. Efficacy results for the two pivotal studies were based on IRC review.

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Covered Clinical Study (Name and/or Number): NP28761

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>344</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>4</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>4</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in Sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>14</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

Clinical Review
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 Alecensa (alectinib)

Covered Clinical Study (Name and/or Number): NP28673

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>304</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>2</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>2</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in Sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

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/s/

ERIN A LARKINS
11/10/2015

GIDEON M BLUMENTHAL
11/10/2015

**MEDICAL OFFICER REVIEW OF BREAKTHROUGH THERAPY REQUEST
DIVISION OF ONCOLOGY PRODUCTS 2 (DOP2)**

IND #:	111723
Proposed use:	Non-small cell lung cancer
Drug Name(s):	RO5424802 (also referred to as AF-802 or CH5424802)
Drug Class:	ALK inhibitor
Drug Type:	Antineoplastic
IND Sponsor:	Hoffmann-La Roche
Primary Reviewer:	Sean Khozin, MD, MPH
Team Leader:	Gideon Blumenthal, MD
Regulatory Project Manager:	Gina Davis

Proposed indication: *RO5424802 is indicated for the treatment of patients who have locally advanced or metastatic non-small cell lung cancer (NSCLC) with ALK-gene rearrangement as detected by an FDA-approved test and have progressed on crizotinib therapy.*

BACKGROUND

Lung cancer is the leading cause of cancer deaths in the United States with an estimated number of new cases of approximately 220,000 and 160,000 deaths in 2012.¹ About 85% of cases are non-small cell lung cancer (NSCLC), the majority of which present as advanced disease (stage IIIB or stage IV) at the time of diagnosis.¹ The median survival of patients with advanced NSCLC with supportive care is about 3 to 6 months.² Standard systemic treatment consists of platinum-based doublet chemotherapy with response rates of about 30% and a median survival of about 10 months.^{3,4,5}

In recent years, clinically relevant molecular subsets of NSCLC with “driver mutations” have been identified. Gene fusion of the Anaplastic Lymphoma Kinase (ALK) with upstream partners (most commonly EML4) is thought to represent an oncogenic event resulting in constitutive activation of the ALK kinase domain. ALK gene rearrangements are found in about 5% of patients with NSCLC.⁶ Crizotinib, an orally available small-molecule inhibitor of ALK and MET tyrosine kinases received accelerated approval by FDA on August 26, 2011. The approval was based on the results of two phase 2 studies enrolling a total of 255 ALK-positive advanced NSCLC patients with objective response rates of 50 and 61% corresponding to a median duration of response (DOR) of 42 and 48 weeks, respectively.⁷ Efforts are underway to characterize mechanisms of acquired resistance to crizotinib, including identification of secondary resistance mutations.⁸

AF802 is an oral ALK inhibitor created by Chugai Kamakura Research Laboratories in Japan. The rights to AF802 in other countries including Europe and the US have been licensed to F. Hoffmann-La Roche. It has shown activity in crizotinib resistant cell lines with secondary gatekeeper mutations and in patients who have progressed on crizotinib.

EFFICACY

Brief summary of planned/ongoing studies:

1. AF-001JP. Ongoing phase 1-2 in Japan.⁹ Total of 70 ALK+ crizotinib-native NSCLC status post progression on chemotherapy enrolled. Overall response (ORR) 93.5% (95% CI 82.1, 98.6%) based on IRC review of 46 scans treated in

- the phase 2 part. Plan to submit for accelerated Japan New Drug Application (NDA) in September 2013 based on the results of this study.
2. AF-002JG/NP28761. Ongoing phase 1 in the U.S. ORR 47.6% in 21 evaluable ALK+ NSCLC patients status post crizotinib and at least one line of chemotherapy.
 3. NP28673. Planned global, open label, single arm, phase 2 study in chemotherapy-failed or naïve, crizotinib-failed, ALK+ NSCLC patients.

AF-001JP

This is a phase 1/2 study, to assess the safety and efficacy of RO5424802. The study is being conducted in 70 **crizotinib-naïve** Japanese patients with locally advanced or metastatic ALK-rearranged NSCLC who have progressed on or after chemotherapy treatment.

Phase 1, dose escalation: 24 patients enrolled at 20-300 mg BID cohorts. No dose limiting toxicities (DLTs) observed.

Phase 2: 46 patients enrolled at the highest dose tested (300 mg BID). Enrollment completed April 18, 2012. ORR based on independent review was 93.5% (Table 1).

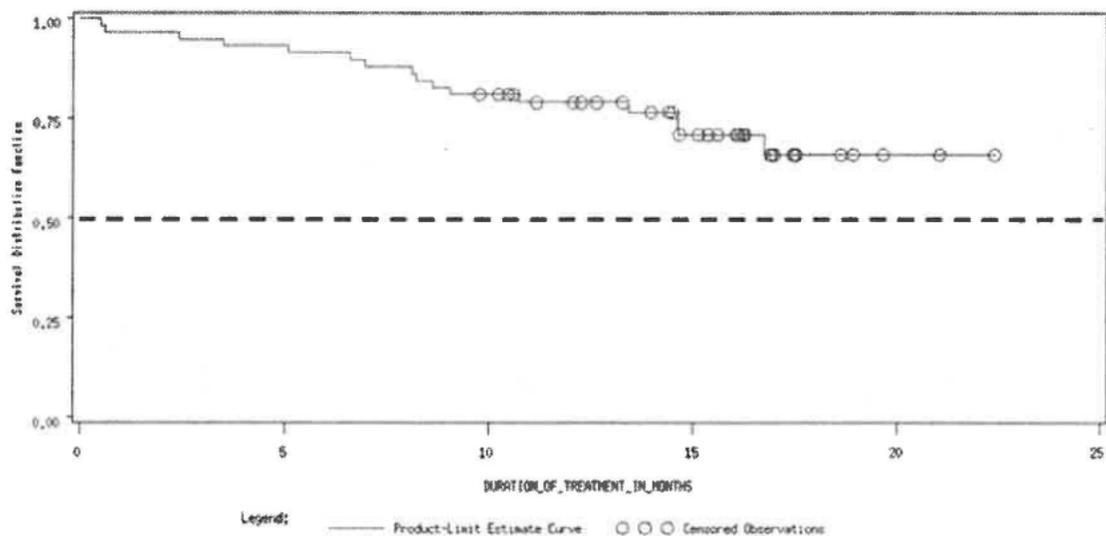
Out of 58 patients who received RO5424802 300 mg BID in the AF-001JP study (12 patients from phase 1 part and 46 patients from phase 2 part) the median duration of response has not been reached. **Error! Reference source not found.** shows progression-free survival in these patients.

Table 1. Independently reviewed response rates (RECIST v1.1) as of March 19, 2013 in the Japanese study AF-001JP in advanced ALK+ NSCLC patients who are crizotinib-naïve

CR	3
PR	40
SD	1
PD	0
NE	2
PR+CR	43
Total	46
ORR	93.5% (82.1-98.6)

CR=complete response, NE=not evaluable, ORR=overall response (PR+CR), PD=progressive disease, PR=partial response, SD=Stable disease
 Median duration of treatment = 14.4 months
 Median duration of response not yet reached

Figure 1. Kaplan-Meier curve of progression-free survival in patients receiving RO5424802 300 mg BID (Study AF-001JP; as of April 18, 2013)



AF-002JG/NP28761

This is an ongoing phase 1/2 study conducted in the U.S.

Population in phase 1 portion:

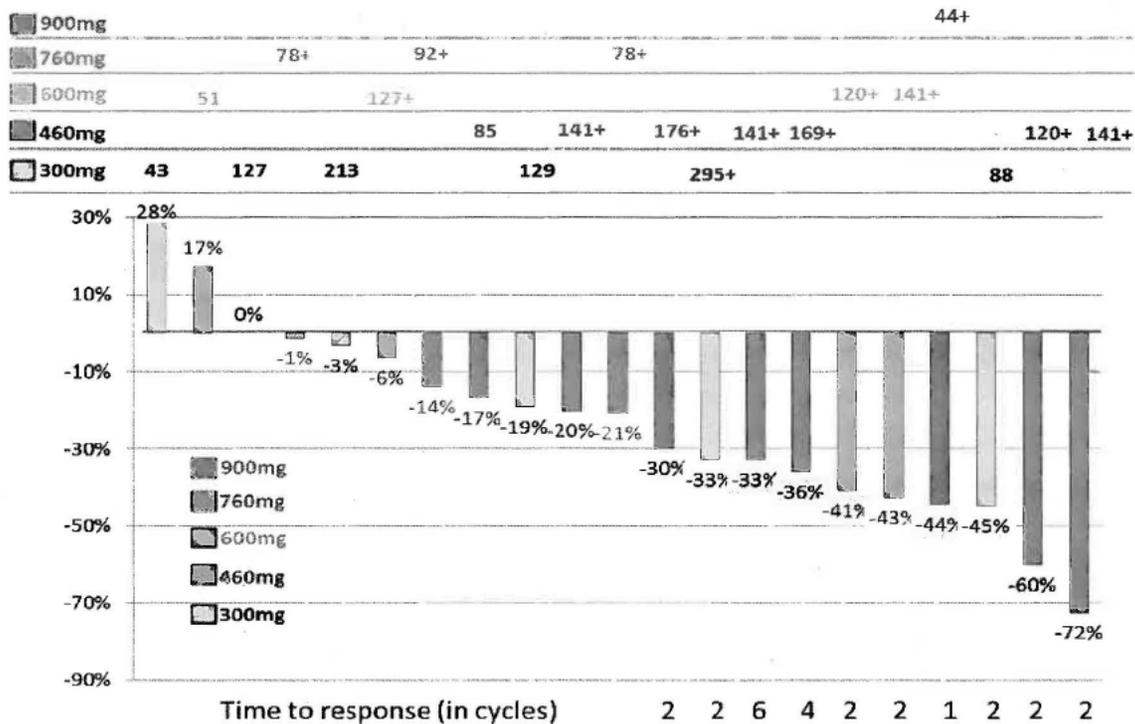
- Advanced NSCLC that has **failed crizotinib** treatment.
- ALK+ by an FDA-approved test. Retest not necessary.

Population in phase 2 portion:

- Sub-population A – Up to 49 locally advanced or metastatic ALK-positive NSCLC patients who have failed crizotinib treatment
- Sub-population B – Up to 15 locally advanced or metastatic ALK-positive NSCLC patients who have never received ALK inhibitor treatment.
 - While in phase 2 portion, protocol was amended in March 2013 to exclude crizotinib-naïve patients.
- Tissue from a post-crizotinib treatment biopsy must be available for ALK diagnosis. If it is not available, patient should have a site of disease amenable to biopsy and consent to a new biopsy procedure and analysis.

In this study, the dose of RO5424802 has been escalated from 300 (N = 7), 460 (N = 7), 600 (N = 6), 760 (N = 6) to 900 (N = 6) mg BID. As of April 17, 2013, no DLTs have been observed. As of April 17, 2013, 32 patients have been enrolled, all of whom have previously progressed on crizotinib and chemotherapy treatment. Eleven out of 21 evaluable patients (at least one follow-up scan available) had brain metastases before treatment, and 3 had prior CNS irradiation. The results of this study have so far showed ORR of 47.6% (26.3% - 68.9%) in 10 of 21 evaluable patients. Six of these ten partial responses have been confirmed. All but one of these responses was ongoing at the time of data cut-off. The median duration of response is not yet available.

Figure 2. Waterfall plot of tumor responses as of April 17, 2013 in the U.S. study AF-002JG/NP28761 in advanced ALK+ NSCLC patients who have failed crizotinib

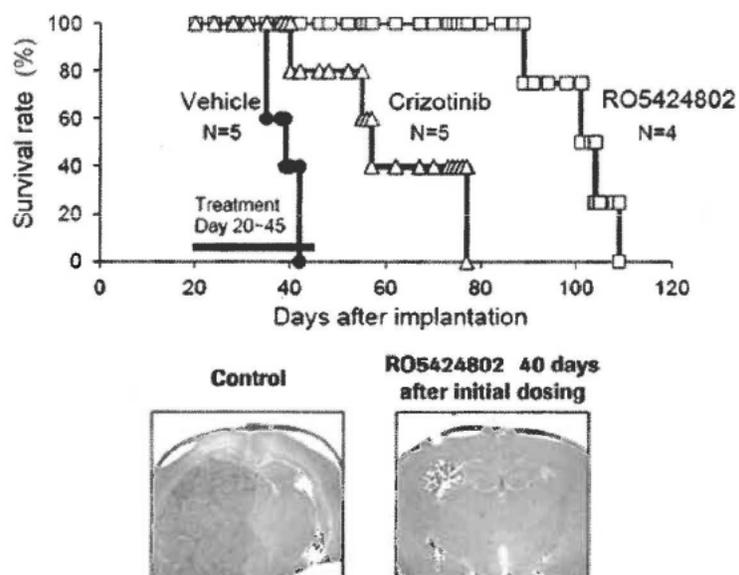


Bars with yellow highlights represent confirmed responses (29%).
 Numbers in the top panel represent duration of treatment with (+) signs indicating ongoing treatment.

The sponsor has presented preliminary evidence on the potential activity of RO5424802 in brain metastasis as follows:

1. The brain-to-plasma ratio of the drug in rats is 0.6-0.8
2. The drug has shown activity in NCI-H2228 (ALK+ NSCLC cells) implanted in the brain of nude mice (Figure 3)
3. No CNS relapses have been seen in phase 2 portion of the Japanese study AF-001JP. The sponsor refers to findings that about 46% of NSCLC patients treated with crizotinib have their first relapse in the CNS.
4. The sponsor reports 3 CNS tumor responses in the US study AF-002JG/NP28761. This study has 11 patients with asymptomatic CNS metastasis at baseline (3 had undergone radiotherapy).

Figure 3. As compared with control (vehicle) or crizotinib, RO5424802 prolongs survival in nude mice with NCI-H2228 (ALK+ NSCLC) cell brain implants



SAFETY

The sponsor presented safety data from the Japanese study AF-001JP. Out of the 70 patients, 58 received 300 mg BID dose and were included in the safety population. More than 40 of them have been on study medication for more than 15 months.

The common adverse events (AEs) with an incidence higher than 10% included dysgeusia (36.2%), constipation (34.5%), nasopharyngitis (31%), rash (29.3%), myalgia (19%), stomatitis (19%), nausea (13.8%) and diarrhea (13.8%). The commonly observed laboratory abnormalities included bilirubin increase (34.5%), aspartate aminotransferase (AST) increase (32.8%), creatinine increase (29.3%), alanine aminotransferase (ALT) increase (25.9%), neutrophil decrease (24.1%), creatinine phosphokinase (CPK) increase (22.4%), white blood cells decrease (19%), blood ALP increase (17.2%) and weight increase (13%). No patients required dose-reduction from 300 mg BID. Twelve patients experienced Grade 3 AEs (2 patients had neutropenia, 2 blood CPK increase, all other Grade 3 treatment-related AEs were observed in one patient only).

Five patients experienced serious AEs and four of them discontinued RO5424802 due to AEs (brain edema, tumor hemorrhage, sclerosing cholangitis, ALT increased, interstitial lung disease).

The observed AEs to date appear to be similar to those seen with crizotinib.

CONCLUSIONS AND RECOMMENDED REGULATORY ACTION

The evidence submitted by the sponsor in support of the proposed indication is limited and based on a small number of patients who have failed crizotinib in the U.S. The majority of the data showing the activity of the drug comes from a foreign study in crizotinib-native Japanese ALK+ NSCLC patients. There is also limited information to fully assess the claimed activity of the drug in ALK+ NSCLC patients with brain

metastasis. The reviewer, however, recommends granting the sponsor's breakthrough designation request based on the following:

- Preliminary evidence of clinical activity of RO5424802 in advanced ALK+ NSCLC patients who have failed crizotinib as demonstrated by ORR of 48% in 21 evaluable patients in an ongoing U.S. phase 1 study.
- Preclinical evidence supporting the activity of RO5424802 in crizotinib-resistant tumors.
- High response rates (94%) in 46 crizotinib-naïve advanced ALK+ NSCLC patients in an ongoing phase 1-2 Japanese study. Responses appear to be durable with the median duration of response not yet reached after a median of 14.4 months of treatment.
- Preliminary evidence of the activity of RO5424802 in patients with CNS metastasis, a common site of relapse in those treated with crizotinib.

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