NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: FDA review was conducted in conjunction with other regulatory authorities under Project Orbis. FDA collaborated with Australian Therapeutic Goods Administration (TGA), Health Canada (HC), Israel's Ministry of Health (IMoH), Switzerland's Swissmedic (SMC), and United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA). While the conclusions and recommendations expressed herein reflect FDA's completed review of the application, the applications may still be under review at the other regulatory agencies.

In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

[FDA will complete this section.]

Application Type	sNDA
Application Number(s)	208434
Priority or Standard	Priority
Submit Date(s)	SDN 752 (September 29, 2023), SDN 757 (October 18, 2023), SDN 765 (November 8, 2023), SDN 768 (November 22, 2023)
Received Date(s)	SDN 752 (September 29, 2023), SDN 757 (October 18, 2023), SDN 765 (November 8, 2023), SDN 768 (November 22 ,2023)
PDUFA Goal Date	May 22, 2024
Division/Office	Division of Oncology 2
Review Completion Date	April 18, 2024
Established Name	alectinib
(Proposed) Trade Name	ALECENSA
Pharmacologic Class	Kinase inhibitor targeting anaplastic lymphoma kinase
Code name	RO5424802
Applicant	Hoffman LaRoche Inc.
Formulation(s)	Capsules, 150 mg
Dosing Regimen	600 mg orally twice daily, with food
Applicant Proposed Indication(s)/Population(s)	ALECENSA is indicated as adjuvant treatment following tumor resection for adult patients with ALK-positive NSCLC, as determined by an FDA-approved test.

Recommendation on Regulatory Action	Traditional Approval
Recommended Indication(s)/Population(s) (if applicable)	ALECENSA is indicated as adjuvant treatment in adult patients following tumor resection of anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) (tumors ≥ 4 cm or node positive), as detected by an FDA-approved test.

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ATC	Anatomical Therapeutic chemical
BICR	Blinded independent central review
BID	Twice a day
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CE	Conformité Européenne
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
CNS	central nervous system
COA	Clinical Outcome Assessment
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CPK	creatine phosphokinase
CRF	case report form
CRO	contract research organization
CRT	clinical review template

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CSR	clinical study report
CSS	Controlled Substance Staff
DFS	Disease-free survival
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
ER	Exposure-response
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
GLP	good laboratory practice
GRMP	good review management practice
HLGT	High Level Group Terms
HLT	High Level Terms
HR	Hazard ratio
HRQoL	Health-related quality of life
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
KM	Kaplan-Meier
MCS	Mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
MID	Minimal important difference
mITT	modified intent to treat
NCA	Non-compartmental Analysis
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NSCLC	non-small cell lung cancer
OCE	Oncology Center of Excellence
OCS	Office of Computational Science
ODD	Orphan Drug Designation
OPQ	Office of Pharmaceutical Quality
OS	overall survival

OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PCS	Physical Component Summary
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PORT	Post-operative radiotherapy treatment
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PS	Performance status
PSUR	Periodic Safety Update report
PT	Preferred Terms
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SMQ	Standardized MedDRA queries
SOC	standard of care
SPM	Second primary malignancies
SRS	stereotactic radiosurgery
TEAE	treatment emergent adverse event
TKI	tyrosine kinase inhibitor
UICC	Union Internationale Contre le Cancer
ULN	Upper limit of normal
US	United States
WBRT	whole brain radiotherapy

1 Executive Summary

1.1. Product Introduction

Alectinib is a tyrosine kinase inhibitor (TKI) that targets anaplastic lymphoma kinase (ALK) and rearranged during transfection (RET), resulting in the inhibition of intracellular signaling pathways involved in tumor cell proliferation and survival.

On December 11, 2015, alectinib was granted accelerated approval for the treatment of patients with ALK-positive metastatic NSCLC whose disease has progressed on or who were intolerant of crizotinib, based on data from two single arm trials.

On November 6, 2017, based on a randomized trial of alectinib versus crizotinib as first-line treatment for metastatic disease, the accelerated approval for alectinib was converted to traditional approval, for the following indication:

Treatment of patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Roche (the "Applicant") has provided substantial evidence of effectiveness supporting the traditional approval of alectinib as adjuvant therapy after tumor resection in adult patients with ALK-positive NSCLC, as detected by an FDA-approved test. The recommendation for traditional approval is supported by results from the ALINA trial, an open-label, randomized, controlled trial evaluating alectinib versus platinum-based chemotherapy for the adjuvant treatment of patients with ALK-positive NSCLC who had complete tumor resection. The primary endpoint is disease-free survival (DFS) as assessed by investigator. Per the statistical analysis plan, DFS was hierarchically tested first in patients with stage II – IIIA disease, followed by DFS in patients with stage IB – IIIA disease (intent-to-treat [ITT] population). ALINA demonstrated a statistically significant and clinically meaningful improvement in DFS in patients with stage II – IIIA disease and in the overall study population (intent-to-treat [ITT] population) in favor of the alectinib arm.

In ALINA, 257 patients with stage IB (tumors ≥4 cm) to stage IIIA NSCLC, per the 7th edition of TNM staging by AJCC, were randomized 1:1 to receive alectinib 600 mg orally twice daily or four cycles of platinum-based chemotherapy. Treatment with alectinib continued until disease progression or unacceptable toxicity, or for up to two years. Crossover was not permitted in the trial.

According to the statistical analysis plan (SAP) for ALINA, a pre-planned interim analysis was conducted after 59 DFS events (approximately 66% information fraction) were observed in the stage II-IIIA subpopulation. At the time of this interim analysis, the hazard ratio (HR) for DFS for patients with stage II-IIIA NSCLC was 0.24 (95% CI: 0.13, 0.45; p-value < 0.0001) favoring alectinib; the median DFS was not reached (NR) (95% CI: not estimable [NE], NE) in the alectinib arm and 44.4 months (95% CI: 27.8, NE) in the chemotherapy arm. Since DFS was positive in patients with stage II – IIIA NSCLC, DFS was tested in the overall ITT population of patients with stage IB (tumors ≥4 cm) – IIIA NSCLC. In the overall population, the HR for DFS was 0.24 (95% CI: 0.13, 0.43; p-value < 0.0001), with median DFS not reached (95% CI: NE, NE) in the alectinib arm and 41.3 months (95% CI: 28.5, NE) in the chemotherapy arm. At the time of the data cutoff date for the current analysis, overall survival (OS) data were immature with6 OS events (alectinib arm: 2/130 deaths; chemotherapy arm: 4/127 deaths) in the ITT population.

The submitted evidence meets the statutory evidentiary standard for traditional approval for the overall study population that included patients with stage IB (tumors ≥4 cm) – IIIA NSCLC. An improvement in DFS has supported prior traditional approvals in the adjuvant setting for NSCLC and other solid tumors such as breast cancer and colorectal cancer. The observed improvement in DFS in the ALINA trial, with a HR of 0.24 in the overall population, is statistically robust and clinically meaningful.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Lung cancer is the leading cause of cancer-related death in the United States (U.S.), with approximately 234,580 new cases of lung cancer expected to be diagnosed in the U.S. in 2024, and approximately 125,070 deaths attributed to lung cancer (Cancer Facts & Figures, 2024). In the U.S., NSCLC represents more than 80% of all lung cancer cases (Howlader N, SEER, 2021). Nearly 50% of patients with newly diagnosed NSCLC present with non-metastatic disease, with approximately 20-25% being candidates for surgery (Waser, Future Oncology, 2022). Historically, adjuvant cisplatin-based chemotherapy has been recommended for patients with stage II-III disease, and for select patients with stage IB disease (per AJCC staging by the 7th edition) with high-risk features, who undergo resection (Pignon JP, J Clin Oncol, 2008). While there have been recent approvals of neoadjuvant and adjuvant treatment regimens using immunotherapy combined with chemotherapy, for the approximate 5% of patients with NSCLC harboring the ALK fusion gene (Pan, Lung Cancer, 2014), the clinical benefit of immunotherapy remains unclear (Gainor, Clinical Cancer Research, 2016). As such, standard adjuvant therapy for patients with resected ALK-positive NSCLC is limited to chemotherapy, and there is an unmet need for adjuvant treatment options in patients with ALK-positive early-stage NSCLC.

Alectinib is a TKI that targets ALK and RET, resulting in the inhibition of intracellular signaling pathways involved in tumor cell proliferation and survival. Alectinib is currently approved in the U.S. for the treatment of patients with ALK-positive metastatic NSCLC.

The primary trial supporting this supplemental new drug application (sNDA) is the ALINA trial, a global, multicenter, open-label, randomized, controlled trial evaluating alectinib versus platinum-based chemotherapy as adjuvant treatment in 257 patients with stage IB (tumors ≥ 4 cm) to stage IIIA (per the 7th edition of TNM staging by the AJCC) ALK-positive NSCLC after complete tumor resection. Patients were randomized (1:1) to receive either alectinib (n=130) or protocol specified platinum-based chemotherapy (n=127; In case of intolerability to a cisplatin-based regimen, carboplatin was administered instead of cisplatin). Study therapy was administered until the completion of the treatment period (24 months for alectinib and 4 cycles for chemotherapy), recurrence of disease, unacceptable toxicity, withdrawal of consent, or death, whichever occurred first. The primary endpoint is disease-free survival (DFS) as assessed by investigator. Per the statistical analysis plan, DFS was hierarchically tested first in patients with stage II – IIIA disease, followed by DFS in the overall population of patients with stage IB (tumors ≥ 4 cm) – IIIA disease (ITT population).

At the time of the pre-specified interim analysis, after 59 DFS events (66% information fraction) were observed in the subpopulation of patients with stage II – IIIA NSCLC, adjuvant alectinib demonstrated a statistically significant and clinically meaningful improvement in DFS over platinum-based chemotherapy for patients with stage II – IIIA NSCLC and for patients with stage IB-IIIA NSCLC (the ITT population). In the stage II-IIIA population, the median DFS was not reached (NR, 95% confidence interval [CI]: not estimable [NE], NE) in the alectinib arm and 44.4 months (95% CI: 27.8, NE) in the chemotherapy arm, with a hazard ratio (HR) of 0.24 (95% CI: 0.13, 0.45; p-value < 0.0001) favoring alectinib. In the ITT population, the median DFS was NR (95% CI: NE, NE) in the alectinib arm and 41.3 months (95% CI: 28.5, NE) in the chemotherapy arm, with a HR of 0.24 (95% CI: 0.13, 0.43; p-value < 0.0001). At the time of the data cutoff date for this interim analysis, OS data were immature with 6 total deaths in the ITT population.

The observed safety profile of alectinib is acceptable in the context of treatment of a life-threatening disease in a curative intent setting. The safety review focused on the 128 patients treated with adjuvant alectinib in the ALINA trial, supported by data from the ALEX study (first-line setting) and Studies NP28761 and NP28673 (second line setting) which evaluated alectinib for the treatment of metastatic NSCLC. In ALINA, the most common (≥20%) treatment-emergent adverse reactions (ARs) observed in the alectinib arm were hepatotoxicity (61%), constipation (42%), myalgia (34%), COVID-19 (29%), fatigue (25%), rash (23%), and cough (20%). Serious adverse reactions (SARs) occurred in 13% of patients in the alectinib arm, with the most common (≥1%) SARs being pneumonia (3.9%), appendicitis (3.1%), and acute myocardial infarction (1.6%). There were no fatal adverse reactions. Permanent discontinuations due to ARs occurred in 5% of patients in the alectinib arm; the most common (≥1%) ARs leading to discontinuation were pneumonitis (2.3%) and hepatotoxicity (1.6%). Key ARs of interest were hepatotoxicity, interstitial lung disease (ILD)/pneumonitis, renal impairment, bradycardia, myalgia and creatinine phosphokinase (CPK) elevation, and hemolytic anemia. While the incidence rates of hepatotoxicity and CPK elevations were higher in ALINA compared to those in the metastatic studies, incidence rates of ILD/pneumonitis, renal impairment, bradycardia, and myalgia were similar between ALINA and the metastatic studies. Hepatotoxicity occurred in 61% of patients treated with alectinib in the ALINA trial, compared to 41% of patients in the overall pooled population of patients treated in the adjuvant and metastatic settings; the incidence of grade ≥3 events was 4.7% in the ALINA trial compared to 8% for the overall pooled population. ILD/pneumonitis occurred in 2.3% of patients in the alectinib arm of ALINA, with grade ≥3 occurring in 0.8% of patients. Renal impairment occurred in 16% of patients treated with alectinib on ALINA, including 0.8% grade ≥3 cases. Bradycardia occurred in 12% of patients treated in the alectinib arm of ALINA, with no grade ≥3 cases. Myalgia was reported in 34% of patients treated with alectinib on ALINA, including, with grade ≥3 occurring in 0.8% of patients. CPK elevation occurred in 77% of patients (including 6% grade ≥3) in ALINA compared to 56% of patients (including 6% grade ≥3) in the overall pooled population. Hemolytic anemia, which was initially reported in the postmarketing setting, was observed in 3.1% of patients in the alectinib arm of ALINA. 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 the review of the application requiring risk management warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use of alectinib.

In summary, the FDA review teams considers the results of the ALINA trial to meet the evidentiary standard for traditional approval and to provide substantial evidence of effectiveness of alectinib as adjuvant therapy for patients with early-stage ALK-positive NSCLC after complete tumor resection. The magnitude of the treatment effect on DFS is statistically significant and clinically meaningful. Based on a favorable risk-benefit assessment for this patient population with serious life-threatening disease being treated with curative intent, the FDA review teams recommend traditional approval for the following indication:

ALECENSA is indicated as adjuvant treatment in adult patients following tumor resection of anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) (tumors ≥ 4 cm or node positive), as detected by an FDA-approved test.

This application was reviewed under Project Orbis and utilizing an Assessment Aid.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Lung cancer is the leading cause of cancer-related death, with more than 80% of lung cancer cases classified as NSCLC. • Of patients with NSCLC, approximately 20-25% present with resectable disease at the time of diagnosis; among these patients, 5-year survival rates are low (ranging from 36% for stage IIIA to 71% for stage IA per AJCC 7th edition [Goldstraw P, J Thorac Oncol, 2016]). • Approximately 5% of patients with NSCLC have tumors harboring the ALK fusion gene.	Early-stage NSCLC is a life-threatening condition with high rates of disease recurrence after surgical resection.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Platinum-based combination chemotherapy is standard of care for adjuvant treatment of resected ALK-positive NSCLC in patients for whom adjuvant treatment is recommended. When the ALINA trial was initiated, NCCN guidelines indicated that adjuvant chemotherapy was recommended for patients with stage II-III NSCLC and should be considered for patients with high-risk stage IB disease (e.g., tumors > 4 cm) per the 7th edition of the AJCC staging system. • In a pooled analysis by the Lung Adjuvant Cisplatin Evaluation (LACE) collaborative group, the overall HR for death in patients with early-stage NSCLC who were treated with adjuvant chemotherapy after resection was 0.89 (95% CI 0.82, 0.96; P=0.005), corresponding to a 5-year absolute benefit of 5.4% from chemotherapy. The HR for DFS was 0.84 (95% CI 0.78, 0.91; P < 0.001). • There have been recent approvals of neo-adjuvant and adjuvant treatment regimens using immunotherapy combined with chemotherapy, but the clinical benefit of immunotherapy remains unclear in the treatment of patients with ALK-positive NSCLC.	Platinum-based doublet chemotherapy is the current standard of care adjuvant therapy for patients with early-stage ALK-positive NSCLC after surgical resection. The comparator treatment in ALINA was appropriate at the time the trial was conducted. While there have been recent approvals of neoadjuvant and adjuvant treatment regimens using immunotherapy combined with chemotherapy, the clinical benefit of immunotherapy remains unclear for patients with ALK-positive NSCLC. There are no approved targeted therapies for use as adjuvant therapy in early-stage ALK-positive NSCLC.
Benefit	• The pivotal trial supporting this sNDA is the ALINA trial, a global, multicenter, open-label, randomized, controlled trial evaluating alectinib versus platinum-based chemotherapy as adjuvant treatment in 257 patients with stage IB (tumors ≥ 4 cm) to stage IIIA ALK-positive NSCLC after complete tumor resection. Patients were treated for up to 24 months for alectinib or up to 4 cycles for chemotherapy. • In the stage II-IIIA population, the median DFS was NR (95% CI: NE, NE) in the alectinib arm and 44.4 months (95% CI: 27.8, NE) in the chemotherapy arm, with a HR of 0.24 (95% CI: 0.13, 0.45), p<0.0001	The submitted evidence meets the statutory evidentiary standard for regular approval with an improvement in DFS corresponding to a HR of 0.24 favoring alectinib over chemotherapy in the overall patient population in the ALINA trial. DFS has been supportive of traditional approvals of adjuvant therapy in NSCLC and other tumor types (e.g., breast cancer, colorectal cancer), and the observed

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	compared to an alpha boundary of 0.0118. • In the ITT population, the median DFS was NR (95% CI: NE, NE) in the alectinib arm and 41.3 months (95% CI: 28.5, NE) in the chemotherapy arm, with a HR of 0.24 (95% CI: 0.13, 0.43), p<0.0001 compared to an alpha boundary of 0.0077. • At the time of the data cutoff date for the current analysis, OS data are immature with 6 total deaths in the ITT population.	magnitude of improvement in DFS in the ALINA trial is statistically significant and clinically meaningful.
Risk and Risk Management	• The primary safety population for this review included patients randomized to the alectinib arm of the ALINA trial with supportive data submitted from previous trials, including the ALEX, NP28761, and NP28673 trials in which alectinib was administered to patients with advanced or metastatic NSCLC. • In the primary safety population of 128 patients in ALINA, the most common (≥20%) adverse reactions (ARs) due to any-cause were hepatotoxicity (61%), constipation (42%), myalgia (34%), COVID-19 (29%), fatigue (25%), rash (23%), and cough (20%). • There were no deaths due to an adverse reaction on the alectinib arm. • Serious adverse reactions (SARs) occurred in 13% of patients in the alectinib arm with most common (≥1%) SARs being pneumonia (3.9%), appendicitis (3.1%), and acute myocardial infarction (1.6%). • Alectinib was discontinued due to ARs in 5% of patients; the most common (≥1%) of these were pneumonitis (2.3%) and hepatotoxicity (1.6%).	The observed safety profile is acceptable when assessed in the context of the treatment of a life-threatening disease. There were no significant safety concerns identified during the review of this application warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS) to ensure the safe use of alectinib. Safety concerns including hepatotoxicity, interstitial lung disease (ILD)/pneumonitis, renal impairment, bradycardia, myalgia and creatinine phosphokinase (CPK) elevation, and hemolytic anemia are adequately addressed by information in the Warnings and Precautions section of product labeling.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as			
			X	Patient reported outcome (PRO)	"Efficacy Results – Secondary or Exploratory Clinical Outcome Assessment (PRO) Endpoints" subsection of Section 8.1.2.
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	□	Other: (Please specify)			
□	Patient experience data that was not submitted in the application, but was considered in this review.				

X

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position: Non–small cell lung cancer (NSCLC) is the most common cause of cancer deaths worldwide with an estimated 1.8 million deaths per year and responsible for the largest proportion of total cancer deaths (18.4%) compared to any other cancer type (World Health Organization 2022). The overall 5-year survival rate for NSCLC ranges from 16%-26% (Cancer Research UK 2020; American Cancer Society 2022). Overall, around 40% of patients with newly diagnosed NSCLC are in the early-stage (Stage I–IIIA) of the disease (Waser et al. 2022; Royal College of Physicians 2021), however, their outcomes are poor, and a significant number of patients relapse and ultimately die as a result of metastatic disease. The 5-year overall survival (OS) rate by pathologic stage (per the Union Internationale Contre le Cancer [UICC]/American Joint Committee on Cancer [AJCC] staging, 7th edition) is 71% for Stage IB, 57% for Stage IIA, 49% for Stage IIB, and 36% for Stage IIIA (Goldstraw et al. 2016).

Approximately 4-5% of patients with NSCLC harbor an anaplastic lymphoma kinase (ALK) fusion gene (Choi et al. 2010; Ou et al. 2012; Paik et al. 2012; Blackhall et al. 2014). ALK-positive NSCLC is a distinct subset of NSCLC. Based on the evidence largely from patients with advanced or metastatic ALK-positive NSCLC, this disease is associated with specific social and clinical features, including never- or light-smoking history, younger age, often economically active with dependents, and tumor histology predominated by adenocarcinomas, and a propensity to develop brain metastases (~50-60% of patients over the course of their disease) (Zhang et al. 2015; Johung et al. 2016). No meaningful difference has been observed in terms of disease prevalence across race-ethnicity groups based on published data to date and no substantial data is available that suggests differences in outcomes of patients with ALK-positive early-stage NSCLC that can be attributed solely to patients' race or ethnicity.

In the early-stage setting, comprehensive biomarker testing is not routinely performed, making it difficult to fully characterize the disease. However, based on limited evidence, patients with ALK-positive early-stage NSCLC generally carry similar clinical features to those observed in metastatic patients. These are more commonly seen in never smokers and younger patients, and more frequently identified at a higher disease stage which suggests that ALK-positive NSCLC has a more aggressive clinical course. Despite receiving standard of treatment care, many ALK-positive early-stage patients still suffer cancer recurrence（Schmid S, et al. 2022).

Recurrence in the brain is particularly associated with the ALK-positive genotype and affects 50-60% of patients during the course of their disease, as compared to 16-20% of ALK-negative patients (Zhang et al. 2015; Johung et al. 2016). Brain metastasis has an adverse impact on patient morbidity and mortality, and leads to significant impairment of quality of life. Brain metastasis can cause a variety of symptoms, including headache, focal neurologic deficits, cognitive dysfunction, seizures, stroke, etc. Current management of brain metastasis involves a multidisciplinary approach including local therapies (such as surgery), stereotactic radiosurgery

(SRS), whole brain radiotherapy (WBRT), and, increasingly, systemic therapy (Eichler and Loeffler 2007; Novello et al. 2016). However, the effectiveness of these conventional local treatment options may be limited due to the presence of microscopic tumor foci not evident on imaging and/or distant cerebral relapse. In addition, SRS can result in acute reactions (due to cerebraledema) and chronic complications of delayed hemorrhage and radiation necrosis (Mathieu et al. 2007; Redmond et al. 2008). WBRT has been associated with neurocognitive decline and late delayed effects have been linked to radiation-induced injury. Systemic therapy with the recently approved new generation of ALK tyrosine kinase inhibitors (TKIs) have demonstrated improved control of brain metastasis, however, patients might be impacted by treatment related side effect (Peters et al. 2017, AT Shaw et al. 2020).

The FDA's Assessment:
Overall, FDA agrees with the Applicant's position. Nearly 50% of patients with newly diagnosed NSCLC present with non-metastatic disease, with approximately 20-25% being candidates for surgery (Waser, Future Oncology, 2022).

2.2. Analysis of Current Treatment Options

The Applicant's Position: For patients with early-stage ALK-positive NSCLC, surgery remains the mainstay of treatment. After surgical resection, the current recommended treatment is adjuvant platinum-based chemotherapy per National Comprehensive Cancer Network (NCCN) guidelines (NCCN 2023). However, in an all-comer population, adjuvant chemotherapy is associated with only modest improvements in patient outcomes: at 5 years, chemotherapy results in ~5% improvement in survival compared with observation; of which most cases of disease recurrence have metastatic spread (Pignon et al. 2008).

Although the treatment landscape has rapidly evolved in recent years with the approvals of cancer immunotherapy regimens, the role of immunotherapy in ALK-positive NSCLC remains unclear. This is because either ALK-positive patients were excluded from most trials or too few had enrolled to allow for a robust assessment of the treatment effect of immunotherapy in ALK-positive early-stage NSCLC. As a result, immunotherapy is generally not recommended in patients with ALK-positive disease.

Progress in the identification of oncogenic driver alterations have provided new opportunities to develop targeted therapeutic agents for the treatment of advanced and metastatic NSCLC (Peters et al. 2017, Lin et al. 2017; Drilon et al. 2020). In the patients with epidermal growth factor receptor (EGFR)-positive NSCLC, EGFR TKIs initially brought significant treatment benefit in the metastatic setting, and more recently in the early-stage setting, where adjuvant treatment with an EGFR TKI demonstrated significant improvement in terms of disease-free survival (Wu et al. 2020). The recent approvals of ALK TKIs have significantly improved outcomes for patients with metastatic ALK-positive NSCLC. However, in the early-stage setting, there are no targeted therapies approved for patients with ALK-positive NSCLC and the currently available therapies are associated with limited benefit. There is an urgent need to

evaluate if ALK TKIs could bring clinical benefit, including delaying cancer recurrence in the CNS for patients with early-stage ALK-positive NSCLC. Thus, there is a high unmet medical need for targeted adjuvant treatment options that offer the possibility of greater efficacy with lesser toxicity than platinum-based chemotherapy, as well as CNS penetration, to potentially delay the onset of CNS recurrence in these patients and improve long-term outcomes.

The FDA's Assessment:
FDA agrees with the Applicant's position that the standard of care therapy for patients with early stage resected ALK-positive NSCLC is adjuvant platinum-based chemotherapy. When the ALINA trial was initiated, NCCN guidelines indicated that adjuvant chemotherapy was recommended for patients with stage II-III NSCLC and should have been considered for patients with high-risk stage IB disease (e.g., tumors > 4 cm) per the 7th edition of the AJCC staging system. Current staging has been updated to the 8th edition of the AJCC staging system. NCCN guidelines now indicate that under the updated 8th edition of the AJCC staging system, patients with stage IIB-IIIB NSCLC and high-risk stage IIA NSCLC should receive adjuvant platinum-based chemotherapy after complete resection if they did not receive a complete course of neoadjuvant chemotherapy. While there have been recent approvals of neoadjuvant and adjuvant treatment regimens using immunotherapy combined with chemotherapy, the clinical benefit of immunotherapy remains unclear for patients with ALK-positive NSCLC.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position: Alectinib was first approved in the United States (US) on 11 December 2015, for the "treatment of patients with ALK-positive, metastatic NSCLC who have progressed on or are intolerant to crizotinib". On 6 November 2017, the indication was extended to "treatment of patients with ALK-positive metastatic NSCLC".

The FDA's Assessment:
FDA agrees with the Applicant's position.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position: An overview of the key regulatory milestones and FDA interactions relevant are provided in Table 1 below.

Table 1 Applicant - Key FDA Interactions Relevant to ALINA

Date	Type of Correspondence	Regulatory History
Jan 27, 2015	Orphan Drug Designation	Alectinib was granted Orphan Drug Designation (ODD) on 27 January 2015 for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC). In addition, alectinib received a full waiver for all pediatric age groups from the requirements of Pediatric Research Equity Act (PREA) for the treatment of NSCLC (Reference ID: 4314373).
Oct 31, 2017	Type B, Pre-Ph3 Meeting	The Agency was in overall agreement with the proposed study design and statistical considerations for Phase 3 study ALINA including the proposed control arm of platinum-based chemotherapy, the treatment duration of 24 months, the primary endpoint of investigator assessed disease-free survival (DFS), the hierarchical testing procedures for the primary endpoint (i.e. the Stage II-IIIA subpopulation followed by the intent-to-treat (ITT) population, which includes patients with Stage 1B-IIIA NSCLC) and the proposed stratification factors (disease stage, race [Asian vs. non-Asian]). The Agency discouraged the inclusion of an interim analysis for DFS (after approximately 67% of target events), however, acknowledged that this was the Sponsor's choice. The Sponsor was encouraged to seek Agency feedback and discuss topline results prior to submitting an supplemental New Drug Application (sNDA) if the interim analysis reads out are statistically significant. The Agency initially disagreed that an sPMA for Ventana ALK IHC (D5F3) would not be required for the assay to be commercially used as a CDx with alectinib in the adjuvant NSCLC setting, however, upon further follow-up between Ventana and CDRH, it was confirmed that an sPMA would not be required.
April 9, 2018	Response to FDA Information Request	Sponsor decided to amend the protocol to exclude Stage IIIA N2 patients who, in the investigator opinion, may require PORT from the ALINA trial as delaying PORT treatment for 2 years in order for patients to complete alectinib treatment would likely result in loss of benefit in a potentially curable population. The Agency agreed with the update and requested that any patients who receive PORT in violation of the protocol design will be recorded as deviations and sensitivity analyses may need to be performed to assess potential effects of differential use of PORT between arms.
October 12, 2018	Response to FDA Information Request	As the Sponsor stated in the Pre-Phase III meeting with FDA that ~75% of ALINA patients would be enrolled from Asian Countries, the Agency requested that the Sponsor provide a detailed plan to enroll a diverse patient population in the ALINA trial that is representative of the U.S. patient population for whom alectinib will be prescribed following its approval. The Sponsor informed the Agency that while only 3 sites will be activated in the U.S., the study also plans to recruit in approximately 160 investigational sites in around 30 countries worldwide. The Sponsor also elaborated that completed analyses have shown that alectinib pharmacokinetics are not influenced by race or ethnicity supporting that similar treatment benefit is expected across patient populations.
October 19, 2021	Response to FDA Information Request	The Sponsor provided clarification that the study is not powered for OS and OS will be analyzed at the time of the interim and primary analyses of DFS to support the benefit-risk assessments. Due to the low accrual of OS events and the lack of historical OS data in the adjuvant ALK-positive setting, the Sponsor proposed to not estimate the number of expected events for the final OS analysis but rather keep the protocol defined final OS analysis at approximately 5 years after the last patient is enrolled.

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

January 12, 2023	Type C, Guidance	The Agency agreed with proposed updated data cuts for studies NP28673, NP28761, and BO28984 to be pooled for the metastatic setting as well as for the overall safety population for presentation within the SCS to contextualize the safety data from ALINA and inform labelling. The Agency also agreed to the Sponsor's proposal to utilize an ISS to provide the source data for the updated data cuts for the aforementioned metastatic studies. The Agency requested that the exposure-response (ER) analyses should explore the relationship between the selected safety parameters and both the parent alectinib exposure and combined exposure of alectinib and its active metabolite M4. However, in a post-meeting follow-up, the Agency agreed to the Sponsor's proposal to conduct ER analyses using combined exposure of alectinib and its active metabolite M4 only as previously submitted reports demonstrated the M4 metabolite has similar in vitro potency and plasma protein binding compared to parent alectinib. The Agency commented that the sNDA filing may meet criteria for RTOR and Project Orbis. The final determination for adequacy will be based on the top-line results and prompted the Sponsor to request a meeting to discuss the adequacy of statistically significant results of an interim DFS analysis. The Agency stated that a blinded independent central review (BICR) audit may be required if the magnitude of DFS results is marginal.
Sept 8, 2023	Informal TC	Informal teleconference to discuss the topline results of ALINA between the Agency and the Sponsor
Sept 18, 2023	Project Orbis	Submission of Project Orbis Global Submission Plan and Sponsor Authorization Forms (IND 111723; Serial No. 0546)
Sept 19, 2023	Type B Meeting Granted Letter	Meeting Request Granted Letter – Type B Meeting from FDA, granting the Sponsor a teleconference pre-sNDA meeting on 27 October 2023 from 2:30 PM to 3:30PM EST (Reference ID: 5247061)
Sept 19, 2023	Pre-meeting Package	Submission of the Pre-Meeting Package for Type B Meeting (IND 111723; Serial No. 0547); Alecensa Adjuvant NSCLC pre-sNDA meeting for ALINA
Sept 22, 2023	RTOR	Email correspondence from the FDA confirming the Sponsor's participation into RTOR
Sept 29, 2023	RTOR	Submission of the first RTOR component for the ALINA sNDA filing
Oct 13, 2023	sNDA Sequence & Project Orbis	Email correspondence from the FDA providing the sequence number for the sNDA (208434/S-015) and confirming the Sponsor's participation into Project Orbis effective 2 September 2023 (PO#114).

The FDA's Assessment:

FDA agrees with the Applicant's timeline of regulatory interactions and assessment that FDA provided feedback and recommendations during these meetings. However, FDA generally does not provide final agreement or endorsement of drug development plans or study design features.

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

4.1. Office of Scientific Investigations (OSI)

FDA performed clinical site inspections at two sites and a data site inspection of Genentech, Inc. (the Applicant). The two investigators were from international sites (Drs. Jin-Seok Ahn [site # 309915, South Korea] and Dae Ho Asan Lee [site # 309916, South Korea]).

Dr. Jin-Seok Ahn enrolled a total of 15 patients (out of 16 screened) to the trial. Four unreported adverse events (AEs) were observed in four patients. There were no deficiencies noted for clinical and tumor assessments for the primary efficacy endpoint of DFS when compared to the data submitted to the sNDA. The unreported AEs were mild in nature and known to be related to alectinib and included in the Prescribing Information (bradycardia, dizziness, edema, liver enzyme and bilirubin election). There was no evidence of patient harm related to these findings. FDA considers the above noted deviations to be unlikely to significantly affect the overall reliability of the safety or efficacy data generated from Dr. Ahn's site.

Dr. Dae Ho Asan Lee screened and enrolled a total of 12 patients to the trial. Three unreported AEs were observed in two patients. There were no deficiencies noted for clinical and tumor assessments for the primary efficacy endpoint of DFS when compared to the data submitted to the sNDA. The unreported AEs were mild and did not appear to be clinically significant and there was no evidence of patient harm related to these findings. FDA considers these deviations to be unlikely to significantly affect the overall reliability of the safety or efficacy data generated from Dr. Lee's site.

The inspection of Genentech assessed the Applicant's oversight responsibilities for Study BO40336 (ALINA). The inspection reviewed site records in full for four clinical sites (Sites #314854, #310751, #311144, and #310778). The inspection observed poor documentation for the receipt of investigational drugs returned from clinical sites, including incomplete records for three out of four sites reviewed (Site #314854, #3310778, and #310751). In addition, there was a failure to provide timely safety reports to participating investigators for four of the six safety reports reviewed [AER3466521 (blood bilirubin increase), AER3473303 (alanine aminotransferase elevation), AER3230337(life threatening anemia), and AER3055323 (acute liver failure)] as required by 21 CFR312.32. However, FDA considers these findings unlikely to impact the efficacy evaluation of the drug. The short delays in reporting safety events to participating investigators were largely due to holidays and there were no unreported serious adverse events.

In addition, the inspection of the Applicant noted a failure to document that decentralized staff (i.e., mobile nursing staff) had appropriate good clinical practice (GCP) training, specifically, four of the ten mobile nurses did not have GCP certificates at the time of their study visits. FDA considers that although the four of ten mobile nurses did not have GCP training certificates, the activities they performed were within their clinical purview.

Furthermore, the scope of mobile nursing use was limited to a total of six clinical sites in Poland (Site #311164), Turkey (Sites #311144, #311146, #311147, and #311223) and US (Site #311504) for 7 patients.

Notwithstanding these findings, the ALINA study appears to have been conducted adequately and the data generated by the inspected clinical investigators and submitted by the Applicant appear acceptable in support of the proposed indication.

4.2. Product Quality

No new CMC information was provided in the supplemental application. Refer to CDER's Quality Review of the current sNDA submission.

4.3. Clinical Microbiology

No clinical microbiology data were submitted in the supplemental application.

4.4. Devices and Companion Diagnostic Issues

Refer to the Center for Devices and Radiological Health (CDRH) review memos by Drs. Erdem Coskun, Soma Ghosh, Donna Roscoe, and Reena Philip for full details.
All patients enrolled to the ALINA trial were required to have ALK-positive NSCLC as determined in accordance with prospective local testing using an FDA-approved and Conformité Européenne (CE)-marked test, with ALK positivity confirmed retrospectively by central testing. If local ALK testing was not available, patients could be tested centrally using the (candidate CDx) Ventana ALK immunohistochemistry (IHC) assay (D5F3).

Ventana ALK IHC (D5F3) has been previously approved as a CDx for crizotinib, ceritinib, lorlatinib, and alectinib (the latter in 2017 for the first-line, metastatic treatment setting).

Given the drug indication statement inclusion of ALK positivity being determined by an FDA-approved test, a CDx device is necessary for this therapy. However, since the Ventana ALK IHC assay (D5F3) is already approved for alectinib in the metastatic setting, a Premarket Approval (PMA) application was not needed for this alectinib indication in the adjuvant setting to update the device Intended Use/Indications for Use.

5 Nonclinical Pharmacology/Toxicology

The Applicant's Position: No new nonclinical data is provided in the current submission, however, a nonclinical safety assessment to support the proposed use of alectinib in the

adjuvant setting considering the ICH S9 Q&A guidance and based on previously submitted nonclinical safety data and available clinical safety data with alectinib is provided in a Nonclinical Overview Addendum (Module 2.4).

The FDA's Assessment:

Alectinib (ALECENSA) is a tyrosine kinase inhibitor that targets anaplastic lymphoma kinase (ALK) and rearranged during transfection (RET). ALECENSA is indicated for the treatment of patients with ALK-positive metastatic non-small cell lung cancer (NSCLC). In the current supplemental application, the Applicant's proposed new indication for alectinib is for the adjuvant treatment of patients with ALK-positive NSCLC following tumor resection.

We agree with the Applicant that no new nonclinical data were provided in the current submission. The Applicant referenced nonclinical data that were previously reviewed by the FDA to support the original approval of ALECENSA for the treatment of patients with ALK-positive metastatic NSCLC.

For the current supplement, the Applicant submitted a nonclinical safety assessment under a Nonclinical Overview Addendum, discussing chronic toxicity, carcinogenicity and developmental and reproductive toxicity (DART), to support the use of alectinib in the proposed adjuvant setting indication. Overall, the FDA does not agree with the Applicant's conclusions that no additional nonclinical studies are needed to support an adjuvant indication for alectinib.

The safety of alectinib was evaluated in up to 13-week duration general repeat-dose toxicology studies in rats and monkeys. In general, we agree that additional long-term general toxicology studies are not warranted based on the available nonclinical toxicology and human safety data. However, considering the proposed younger adult population and the expected prolonged survival, the safety assessment did not adequately address the carcinogenicity potential of alectinib nor the impairment of fertility risk in males and females for the proposed indication.

The Applicant did not conduct studies to investigate the effects of alectinib on fertility. Based on FDA's previous review of the 13-week toxicity studies in rats, oral administration of alectinib resulted in slight glandular atrophy in the prostate (3/10 animals) and seminal vesicles (1/10) at the dose of 27 mg/kg/day (approximately 2.4-fold the estimated $AUC_{0\text{-}24h,ss}$ in humans treated with alectinib 600 mg twice daily); and in monkeys, oral administration of alectinib resulted in minimal interstitial fibrosis in the testis in 1/5 animals at the dose of 12 mg/kg/day (approximately 0.4-fold the estimated $AUC_{0\text{-}24h,ss}$ in humans at the recommended dose of 600 mg twice daily) and minimal lymphocytic cell infiltration in the epididymides (2/10 animals) at ≥4 mg/kg/day (approximately 0.2-fold the estimated $AUC_{0\text{-}24h,ss}$ in humans treated with 600 mg twice daily).
These findings were not observed at the end of an 8-week recovery period. The potential for these findings to impair male fertility was previously discussed, during the initial review of the

NDA in 2015 (see Pharmacology/Toxicology NDA Labeling Review). The Applicant provided data to support the view that the findings were neither adverse nor clearly related to the administration of alectinib but rather a result of a stress response (rat findings) or spontaneous background finding (monkey findings). The FDA agreed based on new data and confirmation from the literature. Therefore, these findings were not included in the alectinib label.

Because of the anticipated prolonged survival in an adjuvant setting and given that alectinib had no adverse effects on male and female reproductive organs in the 13-week toxicity studies, dedicated fertility studies are warranted to assess the possibility of impairment of fertility in males and females of reproductive potential. Post-marketing requirements (PMRs) to conduct fertility studies in male and female rats were communicated to the Applicant. No additional DART testing is needed because embryo-fetal development (EFD) toxicity was already identified and included in the original label. Because ALECENSA can cause fetal harm, FDA included pregnancy testing language under Section 8.3 of label.

During the review process, the Applicant proposed to extend the duration of contraception for females of reproductive potential from 1 week following the last dose to 5 weeks following the last dose to be in line with the Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations Guidance for Industry. According to the guidance, a contraception period of 1 month with an additional 5 half-lives is generally acceptable for aneugenic pharmaceuticals because only dividing oocytes are affected by aneugencity. Considering that alectinib was aneugenic and has a half-life of 30 hours, we agreed with the Applicant's proposed 5-week time frame. Additional minor editorial changes were made to the label to Sections 5.7, 8.1, 8.2, 8.3 and 8.4 to reflect current labeling practices. In consultation with FDA's clinical pharmacology team, the animal to human exposure margins were calculated using PK data from patients with ALK-positive metastatic NSCLC; the geometric mean steady-state area under the curve from 0 to 12 hours ($AUC_{0\text{-}12h}$, ss) was 7430 ng*h/mL and multiplied by 2 to estimate the $AUC_{0\text{-}24h}$, ss in humans to compare with $AUC_{0\text{-}24h}$, ss in male animals.

The Applicant did not conduct carcinogenicity studies to support this supplement. In general, carcinogenicity studies are expected to support an adjuvant indication unless there is evidence of carcinogenic potential in animals and/or patients treated with the drug. Treatment of rats and monkeys with alectinib for 13-weeks did not induce secondary malignancies nor significant proliferative changes. Findings were limited to minimal to slight extension of proliferative zone of mucosa in the stomach and intestine and minimal bile duct hyperplasia. In addition, based on limited to no effects on reproductive organs, no hormonal perturbations were noted. Alectinib was not mutagenic in the bacterial reverse mutation assay or clastogenic in the in vitro Chinese Hamster Lung (CHL) assay but was positive in the in vivo micronucleus assay. A follow up in vivo assay, indicated alectinib is aneugenic showing an increase in numerical rather than structural aberrations. Lastly, the incidence of secondary malignancies in patients treated with alectinib in

the advanced or metastatic setting was within the range of the background incidence of secondary malignancies in the NSCLC population. Given that ALK-positive NSCLC is expected to occur in a younger population (i.e., median age at diagnosis is 52 years), the anticipated prolonged survival for patients with early-stage NSCLC receiving curative-intent therapy, and the absence of evidence of carcinogenicity based on the available nonclinical and clinical safety data, it is important to fully characterize the risk of carcinogenicity for alectinib. Thus, dedicated carcinogenicity studies are warranted to support the use of alectinib in an adjuvant setting. Two PMRs to conduct carcinogenicity studies in mice and rats were communicated to the Applicant. If a 6-month carcinogenicity study in the transgenic mouse is positive, no additional studies will be warranted.

ICH S9 should be used as the starting point for drugs used in the adjuvant setting, as is being proposed for alectinib; however, additional toxicology studies, such as carcinogenicity and DART testing, may be warranted on a case-by-case basis, considering the totality of nonclinical and clinical safety data, the nature of the disease, cure rate and expected time to recurrence. Although the cure and recurrence rate with alectinib for adjuvant treatment are not yet well understood, it is anticipated that alectinib may offer a curative response and prolonged survival in an adjuvant setting. The referenced nonclinical program data are adequate to support approval of alectinib for adjuvant treatment of resected ALK-positive NSCLC; however, given the proposed adjuvant indication, the pharmacology and toxicology team recommend four PMRs to assess the carcinogenic potential of alectinib in mice and rats and to assess the risk of impairment of fertility with alectinib in male and female rats.

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

The Applicant seeks approval of alectinib for the adjuvant treatment of ALK-positive NSCLC in adults. The proposed recommended dosage is 600 mg twice daily (BID) with food, which is the same as that approved for metastatic ALK-positive NSCLC. The proposed recommended dosage appears acceptable based on the clinical data, population pharmacokinetic (PK) analysis and exposure-response relationships for efficacy and safety. Alectinib 600 mg BID demonstrated 76% relative risk reduction of disease recurrence or death compared to chemotherapy. No apparent exposure-response relationship for disease free survival (DFS) was observed and no significant exposure-response relationship was identified for occurrence of Grade ≥ 3 AEs or serious AEs; however, the exposure-response analyses were limited to the proposed dosing regimen. The safety profile in the adjuvant population, including dosage modifications, Grade ≥ 3 AEs, and serious AEs (SAEs), was

consistent with what is known for alectinib in the metastatic setting. Overall, the proposed recommended dosage is supported by the available safety and efficacy data in the adjuvant population.

Recommendations
The proposed recommended dosage of 600 mg BID with food is acceptable and the NDA supplement is approvable from FDA's clinical pharmacology perspective.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position: The key findings from the evaluation of the clinical pharmacology and pharmacokinetics (PK) of alectinib in ALINA (i.e., adjuvant treatment of resected ALK-positive NSCLC), based on a CCOD of 28 February 2023, are as follows:

Characterization of Pharmacokinetics
Observed Pharmacokinetic Concentrations and Non-compartmental Analysis (NCA):

In order to characterize alectinib PK within ALINA, both sparse (all PK-evaluable subjects) and intensive (first six Japanese subjects) PK samples were collected for alectinib and its major metabolite M4.

- Based on the sparse data, the observed steady-state predose concentrations within this study were comparable across visits (i.e., from Week 3 through Week 96). These observed predose concentrations in ALINA were comparable with historic metastatic NSCLC (mNSCLC) data.
- Based on the NCA analysis, the PK of alectinib and M4 in the first six Japanese subjects enrolled in ALINA were comparable with historic mNSCLC data.

Population Pharmacokinetics:

Previously established population pharmacokinetics (popPK) models for alectinib and its major metabolite M4 were able to adequately describe the concentration-time course of alectinib and M4, respectively, in patients with Stage IB-IIIA ALK–positive NSCLC after surgical resection who received 600 mg twice a day (BID) alectinib via external validation. Both alectinib and M4 were characterized by one-compartment models with first-order elimination and with a sequential zero and first-order absorption/formation. Body weight was the only significant covariate affecting the apparent clearance (CL/F) and apparent volume of distribution (V/F) for both alectinib and M4. The effects were incorporated in the models in accordance with the principles of allometric scaling by using a coefficient factor of 0.75 for the CL/F and 1 for the V/F. No other intrinsic or extrinsic factors including race and ethnicity were found to significantly impact alectinib and M4 PK in ALINA.

Exposure Efficacy Relationship

There was no statistically significant exposure-efficacy (disease free survival [DFS]) relationship identified following alectinib 600 mg BID in the adjuvant treatment of resected Stage IB-IIIA ALK-positive NSCLC.

Exposure Safety Relationship

There was no statistically significant exposure-safety (the occurrence of serious adverse event, the occurrence of adverse events of Grade 3 and above) relationship identified following alectinib 600 mg BID in the adjuvant treatment of resected Stage IB-IIIA ALK-positive NSCLC.

The FDA's Assessment: FDA agrees with the Applicant's conclusion that the observed pre-dose concentrations and metabolite-to-parent ratio of alectinib and the M4 metabolite in ALINA were similar to those observed in the previously studied population of patients with metastatic NSCLC. The previously established popPK models for alectinib and M4 were appropriately updated and adequately supported the proposed dosage of 600 mg BID with food. There was no significant exposure-response relationship for safety (i.e., Grade ≥ 3 AEs and SAEs) or efficacy; however, the analyses were limited since no other dosages were assessed in the adjuvant population.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data: ALINA evaluated alectinib administered at 600 mg BID in patients with resected Stage IB (tumors ≥4 cm)-Stage IIIA ALK-positive NSCLC (per the AJCC 7th Edition), herein referred to as Stage IB-IIIA.

The Applicant's position: In line with the ALINA study design, as specified in the protocol, the proposed duration of treatment with alectinib for the new indication is two years, unless there is disease recurrence or unacceptable toxicity. For further details regarding the dose and schedule rationale, please refer to Section 3.3.1. of Protocol BO40336 (Version 7).

The FDA's Assessment: FDA agrees that the proposed recommended dosage of 600 mg BID with food, which is consistent with the current approved labeling, has an acceptable benefit-risk profile in the Stage IB-IIIA ALK-positive NSCLC population. FDA has no objection to the Applicant's position regarding treatment duration.

6.2.2.2. Therapeutic Individualization

Data: Body weight was the only significant covariate in both alectinib and M4 popPK models. The population-predicted area under the plasma concentration–time curve (AUC) at the extremes of body weights observed in the ALINA study (5th and 95th percentiles) were within approximately 27% of that predicted for the median body weight for both alectinib and M4.

The Applicant's Position: When considered in the context of the flat exposure-efficacy and exposure-safety relationships determined over a broad range of exposures observed following

alectinib 600 mg BID, an ~27% increase or decrease in exposure is not expected to have a clinically meaningful impact of safety or efficacy. Therefore, dose adjustment based on body weight is not warranted. Other covariates (sex, age, race, ethnicity, renal impairment, and hepatic impairment) were evaluated, but no covariate was identified to be significant.

The FDA's Assessment:

ALINA included 106, 15, and 3 patients with normal, mild, and moderate hepatic impairment (based on NCI-ODWG hepatic impairment criteria). Due to the limited number of patients with moderate hepatic impairment, FDA analysis could only conclude that there was no clinically meaningful difference in safety of efficacy in patients with mild hepatic impairment. The Applicant's current approved labeling recommendations for patients with hepatic impairment is based on a dedicated study and the Applicant did not provide additional data for the effect of severe hepatic impairment in the adjuvant population. Thus, the current labeling recommendation to adjust the alectinib dosage to 450 mg BID in patients with severe hepatic impairment remains appropriate.

ALINA included 69, 53, and 2 patients with normal, mild, and moderate renal function (based on estimated glomerular filtration rate). Per exposure-response and popPK analyses, there was no clinically relevant difference in PK, efficacy, or safety in patients with mild renal impairment compared to those with normal renal function. Given that less than 1% of the absorbed drug is eliminated in the urine, it is unlikely that mild or moderate renal impairment will have a clinically meaningful effect on alectinib exposure in the adjuvant population. The Applicant did not provide additional data for the effect of severe renal impairment in the target population. FDA has no dosage recommendations for the adjuvant population in patients with renal impairment.

Race had no clinically meaningful effect on alectinib or M4 PK, efficacy, or safety in White (N=53) and Asian patients (N=68) in ALINA. No meaningful conclusion can be reached for Black (N=1) or Hispanic (N=1) patients. FDA has no dosage adjustment recommendations based on race or ethnicity.

Although body weight was found to have a significant effect on the PK of alectinib and M4, there was no clinically significant effect on efficacy or safety. FDA agrees that no dosage adjustment is necessary based on body weight.

6.2.2.3. Outstanding Issues

The Applicant's Position: There are no outstanding issues.

The FDA's Assessment: FDA did not identify any additional clinical pharmacology-related issues.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data: A comparison of alectinib and M4 exposures based on non-compartmental analysis across ALINA (adjuvant NSCLC) and Study BO28984 (ALEX; 1L mNSCLC sNDA 208434) are shown in Table 2. Additionally, comparison of observed alectinib and M4 predose (C_{trough}) concentrations across all the timepoints across the two studies (i.e., ALINA and ALEX) are shown in Table 3.

Table 2 Applicant - Comparison of Alectinib and M4 Pharmacokinetic Parameters based on Non-Compartmental Analysis between ALINA (adjuvant NSCLC) and ALEX (metastatic NSCLC)

	Study	ALINA (N=6)[1]		ALEX (N=9)[2]	
	Analyte	Alectinib	M4	Alectinib	M4
PK Parameter	$T_{max,ss}$ (hr)	7.69 (1.97 - 8.07)	6.82 (0 - 9.55)	4.02 (2.00 - 8.00)	6.00 (2.00 - 10.00)
	$C_{max,ss}$ (ng/mL)	724 (23.7)	304 (33.1)	717 (46.8)	321 (32)
	$AUC_{0\text{-}8h,ss}$ (ng*hr/mL)	4700 (30.2)	1990 (31.4)	5030 (47.2)	2230 (37.0)

Source: ALINA CSR, 1L mNSCLC sNDA 208434
$AUC_{0\text{-}8h,ss}$ = AUC from 0 to time 8 hr at steady state; $C_{max,ss}$ = maximum plasma concentration at steady state;. N =number of participants, $T_{max,ss}$ = time to maximal concentration at steady state.
Descriptive statistics are presented as Geometric mean (geometric mean CV%) for all parameters except $T_{max,ss}$ where it is presented as median (minimum-maximum)
[1] Intensive PK in ALINA was conducted only on the first six Japanese subjects enrolled within the study; Intensive PK in ALEX is presented from the global patient population
[2] Study BO28984 (ALEX) is a Phase III, open-label, randomized, active-controlled, multicenter study of alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive advanced non-small cell lung cancer. See Table 5 for more details.

Table 3 Applicant - Comparison of the Observed Predose (C_{trough}) Concentrations[1] Across Patients and Visits (PK Evaluable Population) between ALINA (adjuvant NSCLC) and ALEX (metastatic NSCLC)

Study	ALINA (N=124)			ALEX (N=135) [3]		
Analyte	Alectinib (ng/mL)	M4 (ng/mL)	M/P ratio[2]	Alectinib (ng/mL)	M4 (ng/mL)	M/P ratio[2]
Mean	661	240	0.405	637	255	0.463
SD	243	91	0.129	261	91.4	0.163
Min	60.3	12.3	0.033	79.4	26.8	0.184
Median	655	238	0.393	626	238	0.430
Max	1330	511	0.968	1470	576	0.997
CV% Mean	36.8	37.9	31.9	41.1	35.8	35.3
Geometric Mean	604	219	0.383	579	238	0.437
CV% Geometric Mean	50.8	52.8	38.4	48.9	41.9	35.1

Source: ALINA CSR, 1L mNSCLC sNDA 208434
CV = coefficient of variation; Geo Mean = Geometric mean; Max = maximum; Mean = arithmetic mean; Min = minimum; M/P = Metabolite/Parent; MW = Molecular Weight; N = number of participants; PK = pharmacokinetic; SD = standard deviation.
[1] For each patient, the median concentration across visits was calculated, and then summary statistics were populated from these median values.
[2] M/P Ratio: Adjusted based on molecular weights for alectinib (MW: 482.62) and M4 (RO5468924) (MW: 456.6)
Note: PK-evaluable population consists of all patients who received any dose of alectinib and who had at least one post-baseline PK sample available.
[3] Study BO28984 (ALEX) is a Phase III, open-label, randomized, active-controlled, multicenter study of alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive advanced non-small cell lung cancer. See Table 5 for more details.

In addition to the observed data, the previously developed popPK models adequately described the alectinib and M4 concentration in patients with Stage IB-IIIA ALK-positive NSCLC after surgical resection who received 600 mg BID alectinib in the ALINA study (popPK report 1127637).

The Applicant's Position: Based on the observed PK data and popPK analysis, alectinib and M4 PK following 600 mg BID dosing regimen were comparable across indications.

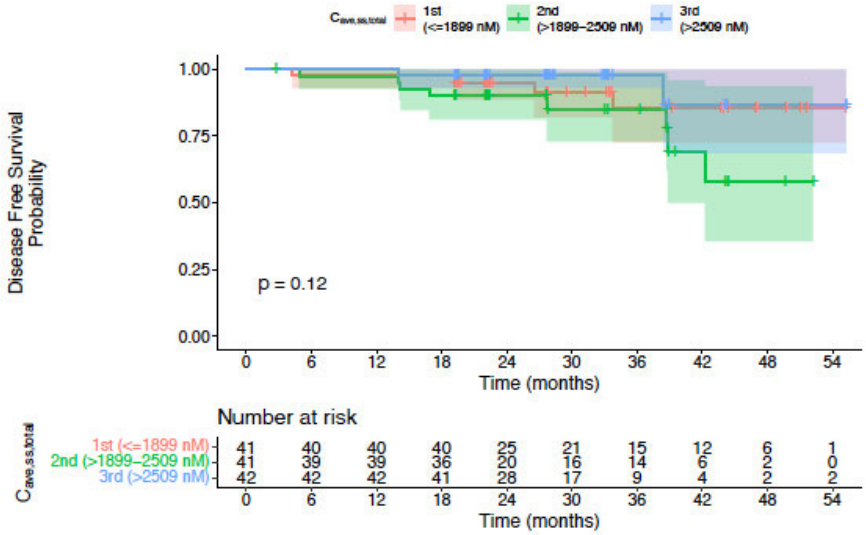
The FDA's Assessment: FDA agrees with the Applicant's conclusion; the PK following 600 mg BID dosing is similar across indications.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

Figure 1 Applicant - Disease Free Survival by Tertiles of Total Alectinib and M4 Exposure (ALINA study) in the intent-to-treat (ITT) Population



Source: *Exposure-response report (RDR: 1127760)*
Cave,ss,total: model-predicted total average plasma concentration of alectinib and M4 at steady state when given 600mgBID
Kaplan-Meier curves of disease free survival (DFS) by tertiles of Cave,ss,total. p-value obtained from the log-rank test.

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

The Applicant's Position: Given the significant clinical efficacy result (the primary endpoint of DFS was met at the pre specified interim analysis; the stratified hazard ratio [HR] =0.24, 95% confidence interval [CI]: 0.13, 0.43; p value < 0.0001; Refer to Section 8.1.2 below) and the flat exposure-efficacy relationship at 600 mg BID, the data provides supportive evidence of effectiveness of the proposed regimen for patients with Stage IB-IIIA ALK-positive NSCLC after surgical resection.

The FDA's Assessment: See Section 6.3.2.2.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data: No evidence of a relationship between total exposure of alectinib and M4 and the primary efficacy endpoint (DFS) was observed. No evidence of a relationship between total exposure of alectinib and M4 and the probability of a serious adverse event or an adverse event of Grade 3 and above occurred in patients in the ALINA study.

The Applicant's Position: Given significant clinical efficacy (HR=0.24; 95% CI: 0.13, 0.43), well-tolerated and generally consistent safety profile with prior mNSCLC studies, and flat exposure-safety and exposure-efficacy relationship when dosed at 600 mg BID in the ALINA study, the evidence supports the proposed regimen of 600mg BID for the general patient population for which the indication is being sought.

The FDA's Assessment: The Applicant did not evaluate dosages other than 600 mg BID in the adjuvant setting; thus, the exposure-response analyses are limited and may not determine whether 600 mg BID is the optimized dosage. FDA agrees that a dosage of 600 mg BID demonstrates a favorable risk-benefit profile in this population.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g., race, ethnicity, age, performance status, genetic subpopulations, etc.)?

Data:

Table 4 Applicant – Exposure of Alectinib and M4 by Patient Factors

		Alectinib ($AUC_{0\text{-}12hr,ss}$) [ng*hr/mL]	M4 ($AUC_{0\text{-}12hr}$, ss) [ng*hr/mL]
Age	<65 years (n=100)	8791 (44%)	3202 (40%)
	>=65 years (n=24)	9693 (32%)	3329 (28%)
Sex	Female (n=72)	9579 (43%)	3633 (38%)
	Male (n=52)	8165 (38%)	2737 (31%)
Race	White (n=53)	7358 (40%)	2856 (40%)
	Black (n=1)	4475	1605
	Asian (n=68)	10520 (35%)	3585 (33%)
	Unknown (n=2)	9894 (17%)	3182 (13%)
Ethnicity	Non-Hispanic (n=121)	9102 (40%)	3273 (36%)

	Hispanic (n=1)	4475	1605
	Unknown (n=2)	4842 (101%)	1920 (103%)
Renal Impairment	Normal (n=69)	8396 (45%)	3077 (39%)
	Mild (n=53)	9895 (36%)	3459 (36%)
	Moderate (n=2)	6010 (6%)	2607 (63%)
Hepatic Impairment	Normal (n=106)	9226 (40%)	3270 (39%)
	Mild (n=15)	7943 (51%)	3139 (33%)
	Moderate (n=3)	5772 (37%)	2295 (37%)
ECOG	0 (n=71)	8137 (44%)	2973 (39%)
	1 (n=53)	10189 (34%)	3599 (34%)
Disease Stage	Stage IB (n=13)	10975 (22%)	3756 (28%)
	Stage II (n=44)	8394 (36%)	3145 (36%)
	Stage IIIA (n=67)	8988 (47%)	3185 (41%)

Source: popPK report (RDR 1127637)
AUC0-12h,ss = popPK-simulated AUC from 0 after last dose to time 12 hr at steady state; n =number of participants.
Descriptive statistics are presented as geometric mean (geometric mean CV%).

Age, Sex, Race and Ethnicity: Age (26 to 80 years), sex, race (White, Black or African American, and Asian) and Ethnicity (Non-Hispanics and Hispanics) did not show clinically meaningful effects on the PK of alectinib and M4, based on popPK analysis (Table 4). There was only one African-American or Black / Hispanic subject enrolled within the study where alectinib and M4 exposures were observed to be 4475 ng*hr/mL and 1605 ng*hr/mL, respectively. These exposures are observed to be within the exposure ranges observed within ALINA when administered at 600 mg BID.

Renal Impairment: Alectinib undergoes minimal renal elimination. Based on popPK analysis, no clinically relevant PK difference was observed in 55 patients with mild or moderate renal impairment compared to patients with normal renal function for both alectinib and M4. Alectinib and M4 PK have not been evaluated in patients with severe renal impairment or renal impairment requiring dialysis (Table 4).

Hepatic Impairment: Alectinib systemic elimination is mainly via hepatic metabolism. Based on popPK analysis, no clinically relevant PK difference was observed in subjects with mild or moderate hepatic impairment relative to subjects with normal hepatic function (Table 4). No patients with severe hepatic impairment were enrolled in ALINA and thus not evaluated within the popPK or ER analyses; however, the current label recommendation for a reduced dose of 450 mg BID for patients with severe hepatic impairment is still considered applicable.

The Applicant's Position: Based on the popPK, exposure-efficacy and exposure-safety analyses, no clinically meaningful covariates were identified that warrant dose adjustment. Therefore, no alternative dosing regimen or management strategy is required for subpopulations based on intrinsic patient factors.

The FDA's Assessment: The Applicant's popPK models adequately described alectinib and M4 PK and dosage adjustments are not necessary for age, ethnicity, race, mild or moderate hepatic impairment, or mild or moderate renal impairment. The current approved labeling recommendation for dosage adjustment in severe hepatic impairment remains appropriate for

this population.

6.3.2.3.1 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data: There are no data to suggest new food-drug or drug-drug interactions with alectinib. Alectinib should be taken with food as stated in the original NDA 208434.

The Applicant's Position: No new information regarding food-drug or drug-drug interaction has been identified in this sNDA submission. The currently labelled food-drug or drug-drug interactions remain applicable.

The FDA's Assessment: Patients in ALINA received alectinib 600 mg BID with food, which is consistent with the current approved labeling. FDA agrees that, with regard to food-drug and drug-drug interaction, the current approved labelling is applicable to the adjuvant population and does not need to be updated.

X	X
Primary Reviewer	Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

Table 5 Applicant - Listing of Clinical Trials Relevant to this sNDA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
ALINA (BO40336)	NCT03456076	Phase III, open-label, randomized, active-controlled, multicenter	Experimental arm: Alectinib 600 mg BID orally taken with food in the morning and evening Control arm: Protocol-defined platinum-based chemotherapy regimens	Efficacy and safety	2 years, or until recurrence of disease, unacceptable toxicity, withdrawal of consent, or death	Total: N = 257 Experimental arm: N = 130 Control arm: N = 127	Patients with completely resected Stage IB (tumors ≥4 cm) to Stage IIIA ALK-positive NSCLC	113 different sites in 26 countries, including the United States
Studies to Support Safety from the Alectinib-treated mNSCLC Patients as Included in the SCS								
NP28761	NCT01871805	Part (Phase) I: Open label, dose escalation Part (Phase) II: Open label, single arm evaluating the recommended Phase II dose	Alectinib 600 mg orally BID in the Phase II portion of the study	Safety, tolerability, efficacy, PK, effect on QT interval of alectinib	Until disease progression, withdrawal of consent, or death	Part 2: N = 87 [1]	Patients with either locally advanced not amenable to curative therapy, or metastatic (Stage IIIB-IV) ALK-positive NSCLC who had experienced disease progression on crizotinib.	27 Sites in US and Canada
NP28673	NCT01801111	Phase I: Open label, dose escalation Phase II: Part 2: Open label, single arm evaluating the	Alectinib 600 mg orally BID in the Phase II portion of the study	Safety, tolerability, efficacy, PK, effect on QT interval of alectinib	Until disease progression, withdrawal of consent, or death	N=138 [1]	Patients with either locally advanced not amenable to curative therapy, or metastatic (Stage IIIB-IV, AJCC 7th edition) ALK-positive NSCLC who have experienced	98 different sites in 29 countries, including the United States

		recommended Phase II dose Part 3: Post-progression treatment MDZ DDI substudy: single sequence crossover study: MDZ SD, alone and in combination with multiple doses of alectinib					disease progression on crizotinib.	
BO28984	NCT02075840	Phase III, open-label, randomized, active-controlled, multicenter	Experimental arm: Alectinib 600 mg BID orally Control arm [2]: Crizotinib 250 mg BID orally	Efficacy, safety, tolerability, pharmacokinetics, patient reported outcomes	Until disease progression or, unacceptable toxicity, withdrawal of consent, or death	Experimental arm: N =152 Control arm [2]: N = 151	Treatment-naive advanced or recurrent not amenable to multimodality treatment, or metastatic (Stage IIIB-IV) ALK-positive advanced NSCLC	83 different sites in 25 countries, including the United States
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)								
Not Applicable								

ALK=anaplastic lymphoma kinase; BID=twice a day; DDI= Drug-Drug Interaction; MDZ=midazolam; NSCLC=non-small cell lung cancer; PK=pharmacokinetics.
[1] NP28673, NP28761 pooled data N = 253: when pooled, 15 patients from midazolam sub-study in NP28673 and 13 patients from Phase I part of NP28761 were included in the count (they received alectinib 600 mg BID).
[2] Only data from the alectinib arm are presented.

The Applicant's Position: The evidence in support of the proposed indication is derived from the pivotal ALINA study (CCOD: 26 June 2023), which is a randomized, active-controlled, multicenter, open-label, Phase III study designed to investigate the efficacy and safety of alectinib (600 mg BID) compared with platinum-based chemotherapy in the adjuvant setting. In addition, pooled safety data from the pooled mNSCLC population (BO28984 [CCOD: 29 November 2019], NP28761 [CCOD: 12 October 2017], and NP28673 [CCOD: 27 October 2017]) and overall pooled safety population (ALINA, BO28984, NP28761, NP28673) are provided as part of the comprehensive safety evaluation of alectinib.

The FDA's Assessment:
FDA agrees with the Applicant's position.

8 Statistical and Clinical Evaluation

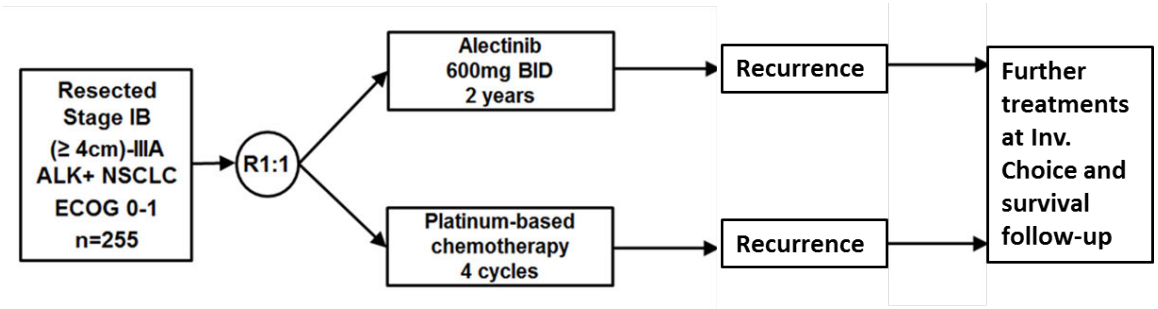
8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. ALINA

Trial Design

The Applicant's Description: ALINA is a Phase III, global, multicenter, open-label, randomized, study comparing the efficacy and safety of alectinib versus platinum-based chemotherapy as adjuvant therapy in patients with completely resected, Stage IB (tumors ≥4 cm)-Stage IIIA, ALK positive NSCLC (as per UICC/AJCC staging system, 7th edition). An overview of the study design is shown in Figure 2.

Figure 2 Applicant - ALINA Study Schema



ALK + = anaplastic lymphoma kinase positive; BID = twice a day; ECOG = Eastern Cooperative Oncology Group (Performance Status); Inv. = investigator; NSCLC = non–small-cell lung cancer; R1:1 = 1:1 randomization.

The FDA's Assessment:

FDA agrees with the Applicant's description of the trial design of ALINA as presented in this section.

Study location: This study was conducted at 113 centers in 26 countries worldwide.

The FDA's Assessment:

FDA acknowledges the trial sites listed above. There was a total of 3 patients in the intent-to-treat (ITT) population enrolled in the US.

Diagnostic criteria: Patients with completely resected (negative margins), histologically-confirmed, Stage IB (tumors ≥4 cm)-Stage IIIA NSCLC, as per UICC/AJCC 7th edition, with documented ALK-positive disease as assessed by an FDA-approved and Conformité Européenne (CE) marked test, who met all required eligibility criteria were randomized in a 1:1 fashion.

Study Treatment and Conduct: Patients in the experimental arm received alectinib at 600 mg

orally BID. Patients in the control arm received one of the protocol-specified platinum-based chemotherapy regimens. In case of intolerability to a cisplatin-based regimen, carboplatin was administered instead of cisplatin.

Study drug (alectinib or platinum-based chemotherapy) was administered until the completion of the treatment period (24 months for alectinib and 4 cycles for chemotherapy), recurrence of disease, unacceptable toxicity, withdrawal of consent, or death, whichever occurred first. Patients who completed a study treatment regimen or discontinued treatment prior to disease recurrence (e.g., due to unacceptable toxicity) continued to be followed until disease recurrence. Data collection continued for each patient until death or study closure, whichever occurred first.

Regular study assessments were performed for both arms during the respective treatment period. The safety follow up visit was performed 28 days after the last dose of alectinib or 28 days after the end of the last cycle of platinum-based chemotherapy. After disease recurrence, patients were treated at the discretion of the investigator according to local clinical practice. No crossover was allowed between the two arms.

Alectinib Dose Selection: The 600 mg BID dosing regimen of alectinib was established as the recommended phase 2 dose (RP2D) based on safety, tolerability, PK, and anti-tumor activity from the dose-escalation part of the Phase I/II Study NP28761. This dosing regimen has been approved in most countries, based on the results of the pivotal Phase II Studies NP28761 and NP28673 in the crizotinib-progressed or intolerant population. The justification of the global alectinib 600 mg BID clinical dosing regimen in the ALK inhibitor–naive population is supported by the observed efficacy and safety results (Peters et al. 2017) and the cumulative available data on alectinib pharmacokinetics and exposure-response from the global patient population in the ALEX study (Hsu et al. 2017).

Blinding: The open-label design of the study was chosen because alectinib is administered orally, whereas the comparator chemotherapies are administered intravenously. Furthermore, infusion times for the different chemotherapy regimens may vary. Blinding of treatments in this scenario would have placed undue burden on both patients and investigators. The Sponsor remained blinded to the treatment assignment information until the boundary for statistical significance of the planned DFS interim analysis which was reviewed by the independent Data Monitoring Committee (iDMC) was crossed.

Administrative Structure: An external iDMC evaluated safety data on an ongoing basis, as well as the pre-specified interim DFS analysis data. All summaries and analyses by the treatment arm for the iDMC review were prepared by an external independent Data Coordinating Center (iDCC). The interim analysis of DFS was conducted in accordance with the methods specified in the Statistical Analysis Plan (SAP). Interactions between the iDMC and Sponsor were carried out as specified in the iDMC Charter.

The FDA's Assessment:

FDA agrees with the Applicant's description of the diagnostic criteria, study treatment and conduct, and alectinib dose selection. In addition, FDA agrees with the description of the rationale for the open-label study design of ALINA and the description of the administrative structure. The interim analysis of DFS was pre-specified in the protocol. The role of an external independent data monitoring committee (iDMC) and external independent Data Coordinating Center (iDCC) was also pre-specified.

Eligibility Criteria

The Applicant's Description: Patients were included in the study if the following key inclusion/exclusion criteria were met:

Key Inclusion Criteria:

- Age ≥ 18
- Complete resection of histologically confirmed, Stage IB (tumor ≥4 cm)-Stage IIIA NSCLC (as per UICC/AJCC, 7th edition)
- Documented ALK-positive disease according to an FDA-approved and CE marked test
- Eastern Cooperative Oncology Group (ECOG) Performance Status of Grade 0 or 1
- Adequate hematologic and renal function as defined per protocol

Key Exclusion Criteria:

- Pregnant or lactating women
- Prior adjuvant radiotherapy for NSCLC
- Prior exposure to systemic anti-cancer therapy
- Prior exposure to ALK inhibitors
- Stage IIIA N2 patients that, in the investigator's opinion, should receive PORT
- Liver disease as defined per protocol
- Patients with symptomatic bradycardia
- History of organ transplant
- Known HIV positivity or AIDS-related illness

The FDA's Assessment:

FDA agrees with the Applicant's description of the eligibility criteria used for enrollment of patients to the ALINA trial.

Study Endpoints

The Applicant's Description: All endpoints described below were analyzed in the Stage II-IIIA subpopulation and the intention-to-treat (ITT) population**.**

Primary Efficacy Endpoint: DFS, defined as the time from randomization to the first documented recurrence of disease or new primary NSCLC as determined by the investigator through use of an integrated assessment of radiographic data, biopsy sample results (if clinically feasible), and clinical status or death from any cause, whichever occurs first.

Secondary Efficacy Endpoints: OS defined as the time from randomization to death from any cause.

Additional Exploratory Efficacy Analyses: Time to CNS recurrence or death (CNS-DFS), defined as the time from randomization to the first documented recurrence of disease in the CNS or death from any cause, whichever occurs first.

The FDA's Assessment:

FDA agrees with the Applicant's description of the primary and secondary endpoints of ALINA. The start of non-protocol adjuvant anti-cancer therapy prior to a DFS event was specified as an intercurrent event and the treatment policy strategy was pre-specified for handling this intercurrent event for the analysis of the primary endpoint of investigator-assessed DFS. DFS was hierarchically tested in patients with Stage II-IIIA NSCLC and then in patients with Stage IB-IIIA NSCLC (the overall intent-to-treat [ITT] population).

OS was not included in the formal hypothesis testing plan controlling for the overall study-wise Type I error rate, and, therefore, the corresponding analyses are considered exploratory only. Additionally, time to CNS recurrence or death was an exploratory endpoint in ALINA.

Statistical Analysis Plan and Amendments

The Applicant's Description: All changes in the planned analyses for the study that were described in the protocol were implemented in the SAP, v2 prior CCOD, which was issued 24 November 2022 and submitted to IND 111723 as Serial 0529. There were no changes after the SAP was finalized.

Analysis Populations:
Efficacy Analysis Populations: The ITT population is defined as all randomized patients with resected Stage IB (tumors ≥ 4 cm)-IIIA NSCLC. The Stage II-IIIA population is defined as all randomized patients with extent of disease as either Stage II or Stage IIIA and is a subset of the ITT population.

Pharmacokinetic-Evaluable Population: Defined as all randomized patients who received any dose of alectinib and who had evaluable pharmacokinetic samples.

Safety-Evaluable Population: Defined as all randomized patients who received any study treatment.

Statistical Methodology: The planned analyses, descriptive comparisons between treatment groups, statistical tests, and determination of sample size are described in the final version of the ALINA SAP v2, Section 4, or contained in the Protocol BO40336 (Version 7), Section 6.

ALINA was designed to demonstrate superiority of alectinib compared with chemotherapy with respect to DFS with 80% power to detect a target HR = 0.55 in the Stage II-IIIA population, and HR = 0.58 (MDD HR = 0.68) in the ITT population (Stage IB-IIIA) in the primary analysis of DFS per investigator. This corresponded to 89 DFS events in the Stage II-IIIA population.

A pre-planned interim analysis was conducted after ~67% of events (59 events) were observed in the Stage II-IIIA subpopulation. The stopping boundaries for the DFS interim analysis were computed with use of the Lan-DeMets approximation to the O'Brien Fleming boundaries. The stopping boundaries for early rejection of the null hypothesis for an overall two-sided 5% significance level were:

- Stage II-IIIA subpopulation: with 59 events, $p \leq 0.0118$
- ITT population: with 65 events, $p \leq 0.0077$

A testing hierarchy was used to control the overall type I error rate at 5% with regards to DFS in the Stage II-IIIA and ITT populations. DFS in the Stage II-IIIA population was first tested at an overall two-sided α level of 0.05. Since a significant effect was observed in the Stage II-IIIA population, DFS in the ITT population was then tested.

Planned subgroup analyses:
The consistency of DFS results in pre-specified subgroups defined by demographic, baseline disease characteristics, and stratification factors was examined.

The FDA's Assessment:

FDA agrees with the Applicant's presentation of the statistical analysis plan for efficacy of ALINA. DFS according to investigator was planned to be hierarchically tested in patients with Stage II-IIIA NSCLC followed by patients with Stage IB-IIIA NSCLC to control the overall study-wise Type I error rate at a two-sided alpha of 0.05. The final analysis of investigator assessed DFS was planned after 89 DFS events in patients with Stage II-IIIA NSCLC, to detect a DFS HR of 0.55 (median 30 vs. 55 months) with 80% power at a two-sided alpha of 0.05. One interim analysis (IA) of DFS was planned after 66% (59/89) of pre-specified DFS events were observed using Lan-DeMets approximation of an O'Brien-Fleming boundary to allocate alpha at the interim and final DFS analyses. DFS by investigator in patients with Stage IB-IIIA NSCLC was planned to be tested at the time of interim and final analyses of DFS in patients with Stage II-IIIA NSCLC. Per FDA calculation, a total of 108 DFS events by investigator was needed to detect a DFS HR of 0.58 (median DFS: 36 vs. 62 months) with 80% power in Stage IB-IIIA NSCLC at a two-sided alpha of 0.05 (IND 111723, Pre-Meeting Package, Date: September 29, 2017).

OS was not planned to be formally tested, but exploratory analyses of OS are to be conducted at the time of the DFS analyses and at the time of the final survival follow-up analysis, which is planned to be conducted at approximately 5 years after the last patient is enrolled.

Protocol Amendments

The Applicant's Description: The first version of the protocol was issued on 05 Feb 2018. Thereafter the protocol was globally amended 6 times; of these, Protocol Version 3 and Version 7 included key changes to the conduct of the study. Protocol was amended to Version 3 on 23 April 2018 to remove Post-operative radiotherapy treatment (PORT) as a treatment option based on prior FDA feedback (Table 3); no patients enrolled into ALINA received PORT. Additionally, to better understand if anemia is associated with hemolysis in patients treated

with alectinib, a systematic monitoring of specific laboratory parameters for hemolytic anemia was introduced in the study for patients treated with alectinib that experience anemia (Grade 2 or higher). Protocol was amended to Version 7 on 16 December 2021 to state that an Independent Review Facility would collect, store, and potentially review imaging and other clinical data (BICR). A comprehensive list of protocol amendments will be included in the CSR.

The FDA's Assessment:

FDA acknowledges the Applicant's description of protocol amendments and agrees with the description of changes for Protocol versions 3 and 7.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant's Position: ALINA was conducted in accordance with the protocol and the principles of the "Declaration of Helsinki" and Good Clinical Practice guidelines. The appropriate Ethics Committees and Institutional Review Boards reviewed and approved the study. The Roche Clinical Quality Assurance group or designee conducted one study audit. In addition, the Roche alliance partner/co-development partners (b) (4) and Chugai performed 1 investigator audit. No critical audit findings were observed. For all audit findings appropriate corrective and preventative actions were undertaken.

The FDA's Assessment:

FDA agrees with the Applicant that the ALINA trial is being conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice guidelines.

Financial Disclosure

The Applicant's Position: For financial disclosure information for the ALINA study presented in the sNDA, please see Module 1.3.4. Additional details of financial disclosures for ALINA are provided in Section 19.2.

The FDA's Assessment:

FDA also references section 19.2 of this Assessment Aid.

Patient Disposition

Data: A total of 257 patients were randomized in the study in 113 sites across 26 countries: 130 in the alectinib arm and 127 in the chemotherapy arm. Of these patients, 9 did not receive study treatment after randomization and were discontinued from the study: 2 patients in the alectinib arm (due to withdrawal of consent) and 7 patients in the chemotherapy arm (due to withdrawal of consent [6 patients] and a protocol deviation [1 patient]).

At CCOD (26 June 2023), the number of patients who had been randomized per country,

followed by the number of centers (in parentheses), is summarized below in descending order: Republic of Korea 49 patients (8), China 45 patients (12), Japan 35 patients (18), Italy 15 patients (5), Russian Federation 15 patients (7), Turkey 15 patients (8), Ukraine 11 patients (5), Poland 8 patients (5), Spain 7 patients (6), Australia 6 patients (3 sites), France 6 patients (4 centers), Germany 6 patients (4 centers), Taiwan 6 patients (5), Austria 5 patients (1), Belarus 5 patients (3), Thailand 5 patients (2), United States 3 patients (3), Denmark 2 patients (1), United Kingdom 2 patients (2), Greece 2 patients (2), Hungary 2 patients (2), Israel 2 patients (2), Romania 2 patients (2), Bosnia and Herzegovina 1 patient (1), Egypt 1 patient (1), Kazakhstan 1 patient (1).

As of the CCOD, study treatment was completed for 77.4% of patients, and ongoing for 10.5% for all patients. A total of 8.9% overall discontinued from the study. In total, 1.5% in the alectinib arm vs. 3.9% in the chemotherapy arm had died. Study treatment had been discontinued for 12.1%. Overall, 5.5% in the alectinib arm vs. 5.0% in the chemotherapy arm discontinued treatment due to AEs (Table 6).

Table 6 Applicant – Patient Treatment Disposition, Safety-Evaluable Patients

	Alectinib (N=128)	Chemotherapy (N=120)	All Patients (N=248)
Completed treatment	84 (65.6%)	108 (90.0%)	192 (77.4%)
Treatment ongoing	26 (20.3%)	0	26 (10.5%)
Discontinued treatment	18 (14.1%)	12 (10.0%)	30 (12.1%)
Adverse Event	7 (5.5%)	6 (5.0%)	13 (5.2%)
Disease Recurrence	8 (6.3%)	0	8 (3.2%)
Other	0	1 (0.8%)	1 (0.4%)
Physician Decision	0	1 (0.8%)	1 (0.4%)
Protocol Deviation	2 (1.6%)	1 (0.8%)	3 (1.2%)
Withdrawal By Subject	1 (0.8%)	3 (2.5%)	4 (1.6%)

Source: t_ds_tx_SE_26JUN2023_40336

Table 7 Applicant – Patient Study Disposition, Intent-to-Treat Patients

	Alectinib (N=130)	Chemotherapy (N=127)	All Patients (N=257)
Received treatment	128 (98.5%)	120 (94.5%)	248 (96.5%)
Study ongoing	123 (94.6%)	111 (87.4%)	234 (91.1%)
Discontinued study	7 (5.4%)	16 (12.6%)	23 (8.9%)
Death	2 (1.5%)	5 (3.9%)	7 (2.7%)
Lost To Follow-Up	0	1 (0.8%)	1 (0.4%)
Protocol Deviation	0	1 (0.8%)	1 (0.4%)
Withdrawal By Subject	5 (3.8%)	9 (7.1%)	14 (5.4%)

Source: t_ds_IT_26JUN2023_40336

The Applicant's Position: The ALINA trial enrolled a diverse population globally through the multi-center, multinational nature of the study.

The FDA's Assessment:

FDA agrees with the Applicant's presentation of distribution of randomized patients by country

and patient disposition as presented in this section. FDA agrees that ALINA was a global trial but notes that enrollment of U.S. patients (1.2%), Black or African American patients (0.4%), and Hispanic or Latino patients (0.4%) was low.

Protocol Violations/Deviations

Data:

Table 8 Applicant – Major Protocol Deviations, Intent-to-Treat Patients

Protocol Deviation Category Protocol Deviation Description	Alectinib (N=130)	Chemotherapy (N=127)	All Patients (N=257)
Total number of patients with at least one major protocol deviation	46 (35.4%)	40 (31.5%)	86 (33.5%)
Total number of major protocol deviations	82	75	157
EXCLUSION CRITERIA			
Total number of patients with at least one deviation	0	2 (1.6%)	2 (0.8%)
Total number of events	0	2	2
Any exclusion criteria for chemotherapy met	0	2 (1.6%)	2 (0.8%)
INCLUSION CRITERIA			
Total number of patients with at least one deviation	9 (6.9%)	4 (3.1%)	13 (5.1%)
Total number of events	9	4	13
ALK-positive disease	1 (0.8%)	1 (0.8%)	2 (0.8%)
Adequate renal function as per protocol	2 (1.5%)	1 (0.8%)	3 (1.2%)
Histologically confirmed Stage IB-Stage IIIA NSCLC	2 (1.5%)	1 (0.8%)	3 (1.2%)
Pregnancy test not done within 3d before 1st dose	2 (1.5%)	1 (0.8%)	3 (1.2%)
Use of contraception according to protocol	2 (1.5%)	0	2 (0.8%)
MEDICATION			
Total number of patients with at least one deviation	15 (11.5%)	5 (3.9%)	20 (7.8%)
Total number of events	16	6	22
Continued treatment when should have discontinued	2 (1.5%)	0	2 (0.8%)
Received expired or quarantined study medication	3 (2.3%)	0	3 (1.2%)
Received incorrect dose of study medication	8 (6.2%)	1 (0.8%)	9 (3.5%)
Received incorrect study medication	0	3 (2.4%)	3 (1.2%)
Received prohibited concomitant medication	1 (0.8%)	0	1 (0.4%)
Treatment with prohibited procedure	1 (0.8%)	1 (0.8%)	2 (0.8%)
PROCEDURAL			
Total number of patients with at least one deviation	35 (26.9%)	34 (26.8%)	69 (26.8%)
Total number of events	57	63	120
Contraception requirements not met	1 (0.8%)	0	1 (0.4%)
Delayed or non-reporting of SAE or AESI	0	1 (0.8%)	1 (0.4%)
ICF amendment with new safety information not signed	6 (4.6%)	8 (6.3%)	14 (5.4%)
Missed disease assessment	19 (14.6%)	23 (18.1%)	42 (16.3%)
Omission of baseline assessment (not eligibility)	3 (2.3%)	4 (3.1%)	7 (2.7%)
Whole panel of lab assessment missed	13 (10.0%)	9 (7.1%)	22 (8.6%)

Source: t_dv_IT_26JUN2023_40336

COVID-19 and Ukraine-Russia Conflict Impact Assessment in ALINA:

The ALINA Study was ongoing at the time of the COVID-19 global pandemic and the Ukraine-Russia Conflict. An assessment was made to evaluate the impact of both these crises on the study. Both were determined to have a minor impact on the study conduct and data analyses were not impacted. Additionally, the benefit-risk ratio can be conclusively established, as both efficacy and safety results were interpretable (full details are provided in CSR Appendix 1 [COVID-19] and Appendix 2 [Ukraine-Russia Conflict]). A list of major protocol deviations are

provided in Table 9 and Table 10, respectively.

Table 9 Applicant – Major Protocol Deviations Related to COVID-19, Intent-to-Treat Patients

Protocol Deviation Category Protocol Deviation Description	Alectinib (N=130)	Chemotherapy (N=127)	All Patients (N=257)
Total number of patients with at least one major protocol deviation	13 (10.0%)	11 (8.7%)	24 (9.3%)
Total number of major protocol deviations	20	12	32
MEDICATION			
Total number of patients with at least one deviation	1 (0.8%)	0	1 (0.4%)
Total number of events	1	0	1
Received incorrect dose of study medication	1 (0.8%)	0	1 (0.4%)
PROCEDURAL			
Total number of patients with at least one deviation	13 (10.0%)	11 (8.7%)	24 (9.3%)
Total number of events	19	12	31
ICF amendment with new safety information not signed	2 (1.5%)	0	2 (0.8%)
Missed disease assessment	9 (6.9%)	10 (7.9%)	19 (7.4%)
Whole panel of lab assessment missed	4 (3.1%)	1 (0.8%)	5 (1.9%)

Source: t_dv_COVDV_IT_26JUN2023_40336

Table 10 Applicant – Major Protocol Deviations Related to Ukraine-Russia Crisis, Intent-to-Treat Patients

Protocol Deviation Category Protocol Deviation Description	Alectinib (N=130)	Chemotherapy (N=127)	All Patients (N=257)
Total number of patients with at least one major protocol deviation	0	4 (3.1%)	4 (1.6%)
Total number of major protocol deviations		9	9
PROCEDURAL			
Total number of patients with at least one deviation	0	4 (3.1%)	4 (1.6%)
Total number of events		9	9
ICF amendment with new safety information not signed	0	1 (0.8%)	1 (0.4%)
Missed disease assessment	0	4 (3.1%)	4 (1.6%)

Source: t_dv_UKRDV_IT_26JUN2023_40336

The Applicant's Position: Overall, the frequency and types of major protocol deviations were generally similar between the treatment arms, although more deviations related to study medication were reported in the alectinib arm, which was largely due to longer treatment duration but also due to administration frequency and route (daily capsules vs infusion every 21 days) of alectinib vs chemotherapy. Sensitivity analyses were conducted to assess the impact of missing disease assessments on DFS, the results were consistent with those observed in the primary analysis. None of the major protocol deviations led to exclusion of data from the analysis, posed an increased safety risk to any the patient, or were considered to have affected the integrity of the study findings. In addition, the COVID-19 pandemic disruption and the Ukraine-Russia conflict had a minor impact on study conduct and did not impact the overall data quality or outcome of the study.

The FDA's Assessment:

While, in general, FDA agrees with the Applicant's description of the impact of the major protocol deviations on the trial outcome, the proportion of patients with protocol deviations due to missed disease assessments in ALINA is relatively high (14.6% in alectinib arm and 18.1% in chemotherapy arm). In a response to an FDA information request (submitted to the FDA on February 28, 2024, under Seq# 597), the Applicant provided further information on the missing disease assessments including reasons for missing disease assessments as presented below:

Table 11 FDA – Reasons for missing disease assessments

Reason for "Missing Disease Assessment" protocol deviation	Alectinib	Platinum-Based Chemotherapy	Grand Total
Not applicable - deviation category was reported incorrectly	1	0	1
Patient did not perform scan due to hospitalization	0	1	1
Patient did not perform scan due to new bladder cancer and pursue other treatment	0	1	1
Patient did not perform scan due to patient's preference of follow-up in local hospital	1	0	1
Patient did not perform scan without reason reported	5	4	9
Patient left the country	1	0	1
Patient-related issue	0	1	1
Site action due to epidemic/pandemic	4	4	8
Site-related issue	3	4	7
Subject movement restricted due to epidemic/pandemic	8	4	12
Ukraine crisis	1	1	2
Unavailability of MRI machine	1	1	2
Grand Total	25	21	46

[1]All counts represent patients. Multiple occurrences of the same reason in one individual are counted once.

Source: Response to FDA information request (submitted to the FDA on February 28, 2024, under Seq# 597).

The most common reason for missed disease assessments, accounting for 43% of missed disease assessments, was related to the COVID-19 pandemic (i.e., "site action due to

epidemic/pandemic" or "subject movement restricted due to epidemic/pandemic). Approximately 20% of missed disease assessments were due to unknown reasons.

Per the FDA Guidance to Industry *Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics*, for time-to-event endpoints, patients with events after an extended loss to follow-up-time (e.g., two or more consecutive missed assessments) should be censored at the time of the last adequate assessment. However, according to the Applicant there was only one patient in the chemotherapy arm who had two consecutive missed disease assessments prior to a DFS event.

The ALINA statistical analysis plan (SAP) version 2.0, issued on February 24, 2022, included a plan for DFS censoring data from sites in Russia and/or Ukraine, due to the discontinuation of the trial in Russia and Ukraine by the end of June 2022, as a result of increased logistical challenges of ensuring continuity of care for study patients during the Ukraine-Russia conflict. A total of 30 patients from Russia were impacted and had a short duration of follow-up. A sensitivity analysis excluding the 30 patients was also planned. SAP version 2.0 also included a plan to summarize COVID-19 related major protocol deviations by treatment arm.

Overall, the reported protocol deviations do not appear to be a significant cause of bias influencing the study results.

Table of Demographic Characteristics

Data: In the ITT population, demographics and baseline characteristics were generally well balanced between the alectinib and chemotherapy arms. Compared with the chemotherapy arm, the alectinib arm had a higher proportion of female patients (57.7% in the alectinib arm vs. 46.5% in the chemotherapy arm) and never-smokers (64.6% vs. 55.1%, respectively).

The study population was evenly balanced between male patients (47.9%) and female patients (52.1%), with a median patient age of 56.0 years (range: 26-87 years). Most patients (76.3%) were <65 years of age. All patients had a baseline ECOG performance status (PS) of 0 (53.3% overall) or 1 (46.7% overall), and most were never smokers (59.9%).

Table 12 Applicant - Demographic Characteristics

	Alectinib (N=130)	Chemotherapy (N=127)	All Patients (N=257)
Age (yr)			
n	130	127	257
Mean (SD)	53.4 (12.5)	56.6 (11.3)	54.9 (12.0)
Median	54.0	57.0	56.0
Min - Max	26 - 80	33 - 87	26 - 87
Age group 1 (yr)			
n	130	127	257
<65	103 (79.2%)	93 (73.2%)	196 (76.3%)
>=65	27 (20.8%)	34 (26.8%)	61 (23.7%)
Sex			
n	130	127	257
Male	55 (42.3%)	68 (53.5%)	123 (47.9%)
Female	75 (57.7%)	59 (46.5%)	134 (52.1%)

Ethnicity			
n	130	127	257
Hispanic or Latino	1 (0.8%)	0	1 (0.4%)
Not Hispanic or Latino	127 (97.7%)	122 (96.1%)	249 (96.9%)
Not Stated	2 (1.5%)	2 (1.6%)	4 (1.6%)
Unknown	0	3 (2.4%)	3 (1.2%)
Race (eCRF)			
n	130	127	257
Asian	72 (55.4%)	71 (55.9%)	143 (55.6%)
Black or African American	1 (0.8%)	0	1 (0.4%)
White	55 (42.3%)	52 (40.9%)	107 (41.6%)
Unknown	2 (1.5%)	4 (3.1%)	6 (2.3%)
Race (IxRS)			
n	130	127	257
Asian	72 (55.4%)	71 (55.9%)	143 (55.6%)
Non-Asian	58 (44.6%)	56 (44.1%)	114 (44.4%)
ECOG performance status at baseline			
n	130	127	257
0	72 (55.4%)	65 (51.2%)	137 (53.3%)
1	58 (44.6%)	62 (48.8%)	120 (46.7%)
Tobacco use history			
n	130	127	257
Never	84 (64.6%)	70 (55.1%)	154 (59.9%)
Current	5 (3.8%)	3 (2.4%)	8 (3.1%)
Previous	41 (31.5%)	54 (42.5%)	95 (37.0%)

Source: t_dm_IT_26JUN2023_40336

The Applicant's Position: Based on published data to date and considering the rarity of ALK-positive disease itself, no difference has been observed in terms of disease prevalence across race-ethnicity groups. Through the multiregional recruitment approach taken in the ALINA study, the demographics of patients enrolled were generally representative of the broad distribution of ALK-positive disease and by whom alectinib will be used. The demographics were also generally well balanced between treatment arms in the ITT population.

The FDA's Assessment:

In general, FDA agrees with the Applicant's presentation of patient characteristics in ALINA but notes that there were more females in the alectinib arm (58%) compared to the chemotherapy arm (46%) and more never-smokers in the alectinib arm (65%) compared to the chemotherapy arm (55%). FDA subgroup analyses in males, females, non-smokers, and smokers (Table 17), indicated that these imbalances in sex and smoking status between treatment arms did not impact the overall study results and interpretation of the results.

FDA also notes that enrollment of Black or African American patients (0.4%) and Hispanic or Latino patients (0.4%) was low. While the true incidence of ALK positive NSCLC across racial and ethnic subgroups in the U.S. is not well characterized, which may in part be related to inconsistent tumor genomic testing, Black or African American and Hispanic or Latino patients were underrepresented in ALINA. However, given the pathophysiology of ALK positive NSCLC and alectinib's mechanism of action as a TKI targeting an oncogenic driver mutation, it is expected that the treatment effect of alectinib will be consistent across racial and ethnic subgroups. Race and ethnicity are not expected to have clinically meaningful effects on the PK of alectinib.

Other Baseline Characteristics

Data: The majority of patients in the ITT population (54.9%) had Stage IIIA disease and non-squamous histology (96.5%). The median time between NSCLC diagnosis to randomization in ALINA for all patients in both arms was around 2.0 months (range: 0.4 months-13.1 months).

All patients in the study were required to undergo a complete resection of their tumor prior to receiving study treatment. The total number of surgeries and type of procedures was comparable between treatment arms, with lobectomy being the most commonly reported procedure (96.9% in the alectinib arm vs. 92.1% in the chemotherapy arm). The median time between complete resection of NSCLC to randomization was similar in both arms (1.68 months [range: 1.0-2.8 months] in the alectinib arm vs. 1.74 [range: 1.0-2.8 months] in the chemotherapy arm).

The Applicant's Position: Baseline and disease characteristics were generally well balanced between treatment arms in the ITT population.

The FDA's Assessment:

FDA agrees with the Applicant's presentation of the baseline disease characteristics in this section. ALINA included patients with completely resected (negative margins), histologically confirmed Stage IB (tumors ≥ 4 cm) to Stage IIIA NSCLC as per the American Joint Committee on Cancer (AJCC) 7th edition. Patients were enrolled on ALINA based on the 7th edition of the AJCC TNM staging system. However, in 2018, the AJCC staging system was updated to the 8th edition, which is the staging system that is currently in use. Based on the updated staging system, the following groups of patients enrolled to ALINA per AJCC 7 would be considered to have higher stages of disease per AJCC 8 as shown in the table below:

Table 13 FDA – Lung Cancer Staging per AJCC 7th and 8th Editions

Tumor (T) Component	AJCC 7th Edition	AJCC 8th Edition
>3 – 4 cm	T2a	T2a
>4 – 5 cm	T2a	T2b
>5 – 7 cm	T2b	T3
>7 cm	T3	T4

*There were no changes to the Node (N) component between the 7th and 8th editions of the AJCC TNM staging systems.

The distribution of tumor stage in the ALINA trial by the AJCC 7th and 8th editions is provided below. Six percent of the overall patient population were classified as stage IB under the AJCC 7th edition but would be re-classified as stage IIA per the AJCC 8th edition, and 5% of patients

were classified as stage IIIA under the AJCC 7th edition but would be re-classified as stage IIIB per the AJCC 8th edition.

Table 14 FDA – The Concordance Analysis of the AJCC 7th and 8th Edition Staging Categorization

	AJCC 8th Edition					
AJCC 7th Edition	Stage IB	Stage IIA	Stage IIB	Stage IIIA	Stage IIIB	Total
Stage IB	11 (4.3%)	15 (6%)	0	0	0	26 (10%)
Stage IIA	0	0	80 (31%)	0	0	80 (31%)
Stage IIB	0	0	4 (1.6%)	6 (2.3%)	0	10 (3.9%)
Stage IIIA	0	0	0	128 (50%)	13 (5%)	141 (55%)
Total	11 (4.3%)	15 (6%)	84 (33%)	134 (52%)	13 (5%)	257 (100%)

Source: FDA analysis of the Applicant submitted data ADSL. DCO: June 26, 2023.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data: The majority of patients in the ITT population (96.5%) received at least one concomitant medication (96.2% in the alectinib arm vs. 96.9% in the chemotherapy arm). The most frequently used concomitant medications (by proportion of patients in the alectinib arm vs. the chemotherapy arm) by Anatomical Therapeutic chemical (ATC class Level 2) (WHODRUG GLOBAL B3 dictionary) was Ophthalmologicals (53.8% vs. 87.4%).

In the ITT population, 12.3% from the alectinib arm vs. 30.7% from the chemotherapy arm received any subsequent follow up anti-cancer systemic therapy after ending the study treatment period. Off-study alectinib or 'alectinib hydrochloride' was the most commonly used agent by patients from both arms (3.8% in the alectinib arm vs. 22.8% in the chemotherapy arm). In total 3.8% in the alectinib arm vs. 7.1% in the chemotherapy arm, received follow-up radiotherapy with the brain the most common site (1.5% in the alectinib arm vs. 3.9% in the chemotherapy arm). Follow up cancer surgery was reported in a small proportion (0.8% in the alectinib arm underwent surgery at a location in bone, while 2.4% in the chemotherapy arm underwent surgery at locations reported as bone, brain, and lymph node (1 patient each).

The Applicant's Position: Overall, the concomitant treatments administered were not considered to have impacted the study results. Most of the patients from the ALINA study who received follow up anti-cancer systemic therapy, received ALK TKIs as their subsequent therapies. The most commonly used ALK TKIs were second and third generation ALK TKIs, including alectinib, brigatinib, lorlatinib, and ceritinib. Off-study alectinib or 'alectinib hydrochloride' was the most commonly used ALK TKI. This is consistent with the clinical practice of the US where several ALK TKIs have been approved in the metastatic setting, with the second

and third generation ALK TKIs being the preferred option per the NCCN guidelines, and were accessed by ALINA patients who experienced cancer recurrence.

The FDA's Assessment:
FDA agrees with the Applicant's assessment regarding treatment compliance, concomitant medications, and rescue medication use. Patients who received follow-up anti-cancer systemic therapy generally received therapy in line with standard of care.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

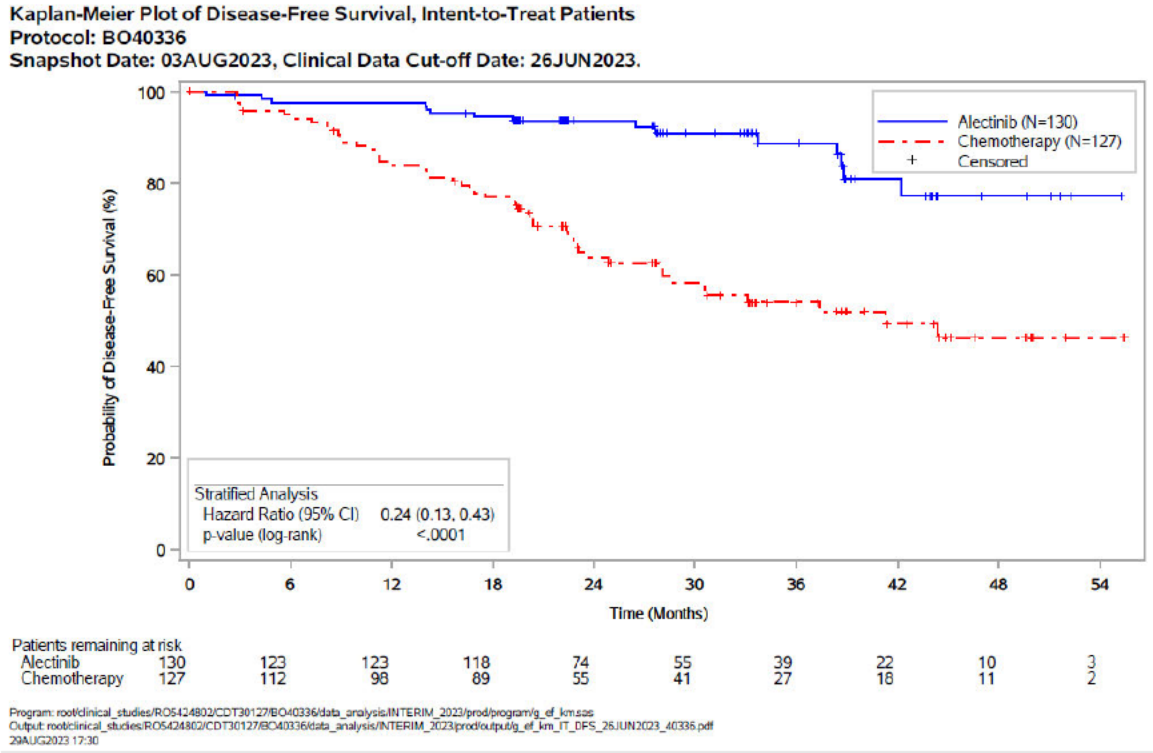
Data: As of the CCOD (26 June 2023), the median duration of survival follow-up of 27.8 months (27.8 months for the alectinib arm vs. 28.4 months for the chemotherapy arm.

The primary endpoint was met for both the Stage II-IIIA subpopulation and the ITT population. In the ITT population, 15 patients (11.5%) in the alectinib arm vs. 50 patients (39.4%) in the chemotherapy arm had experienced disease recurrence or death. The primary endpoint of INV-DFS was met at the pre specified interim analysis. The stratified HR was 0.24 (95% C: 0.13, 0.43; p value < 0.0001), which corresponds to a 76% relative risk reduction of disease recurrence or death with alectinib compared to chemotherapy.

The median DFS was not reached in the alectinib arm and was 41.3 months (95% CI: 28.5, NE) in the chemotherapy arm. The Kaplan-Meier (KM) curves began to separate at approximately 3 months after randomization in favor of the alectinib arm and was maintained thereafter. A higher proportion of patients were alive and disease-free in the alectinib arm when compared to the chemotherapy arm at 2 years (93.6% vs. 63.7%, respectively), and at 3 years (88.7% vs. 54.0%, respectively; Figure 3). Results for the Stage II-IIIA subpopulation were similar to results in the ITT population.

Additionally, the observed alectinib treatment effect was generally consistent across the pre-specified subgroups. Results of the sensitivity analyses to assess the impact of stratification errors, missing disease assessments, and Ukraine-Russia conflict were consistent with those observed in the primary analysis in the ITT population and Stage II-IIIA subpopulation and support the observed DFS benefit of alectinib over chemotherapy.

Figure 3 Applicant - Kaplan-Meier Plot of Disease-Free Survival, Intent-to-Treat Patients



The Applicant's Position: ALINA met its primary endpoint of investigator assessed DFS at the pre-planned interim analysis, demonstrating statistically significant and clinically meaningful improvement for alectinib compared to platinum-based chemotherapy as adjuvant treatment in both the Stage II-IIIA population, and the ITT population. The observed DFS benefit of alectinib over chemotherapy was clinically meaningful across pre-specified subgroups, including across race (Asian vs. Non-Asian).

The FDA's Assessment:

In general, FDA agrees with the Applicant's description of the investigator-assessed DFS results in patients with Stage II-IIIA NSCLC and in the ITT population. FDA also notes the following:

1. The primary endpoint, investigator-assessed DFS, was hierarchically tested first in patients with Stage II-IIIA NSCLC followed by in the ITT population. Statistically significant DFS results were observed in both the Stage II-IIIA NSCLC sub-population and in the ITT population. The efficacy results and the corresponding Kaplan-Meier plots are provided in Table 15 and Figure 4, respectively.

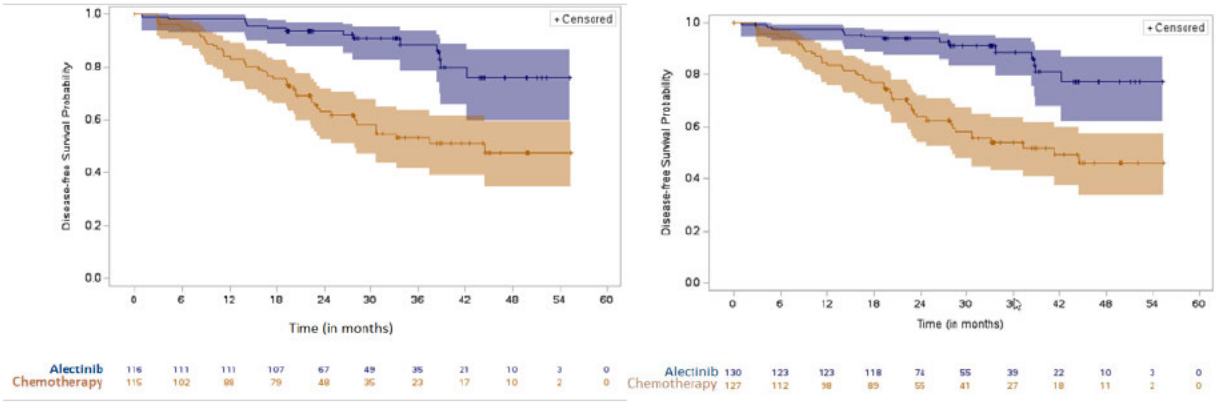
Table 15 FDA – Analysis of the primary endpoint: investigator-assessed disease-free survival (DFS)

	Stage II-IIIA sub-population		ITT	
	Alectinib N=116	Chemotherapy N=115	Alectinib N=130	Chemotherapy N=127
Disease recurrence (%)	14 (12%)	44 (38%)	15 (12%)	49 (38%)
Death (%)	0	1 (0.87%)	0	1 (0.78%)
Median, months (95% CI)[1]	NR (NE, NE)	44.4 (27.8, NE)	NR (NE, NE)	41.3 (28.5, NE)
Hazard Ratio (95% CI)[2]	0.24 (0.13, 0.45)		0.24 (0.13, 0.43)	
p-value[3]	<0.0001		<0.0001	

[1]Kaplan-Meier method; [2]Stratified Cox model stratified by race (Asian vs. other races) in Stage II-IIIA and stratified by race (Asian vs. other races) and tumor stage (Stage IB vs. II vs. IIIA) in ITT; [3]stratified log-rank test stratified by race (Asian vs. other races) in Stage II-IIIA and stratified by race (Asian vs. other races) and tumor stage (Stage IB vs. II vs. IIIA) in ITT.

Source: FDA analyses of the Applicant submitted data ADTTE. DCO: June 26, 2023.

Figure 4 FDA – Kaplan-Meier Plot of Investigator-assessed DFS in Stage II-IIIA NSCLC (left) and in ITT population (right)



Source: FDA analyses of the Applicant submitted data ADTTE. DCO: June 26, 2023.

2. In general, FDA recommends that patients who receive a new anti-cancer therapy be censored at the time of receipt of the new anti-cancer therapy. However, in ALINA, start of non-protocol adjuvant anti-cancer therapy prior to a DFS event was specified as an intercurrent event for which the treatment policy strategy was employed in the primary analysis.. In a response to FDA information request (submitted to the FDA on February 28, 2024, under Seq# 597), the Applicant indicated that there were only 3 patients who had received new anti-cancer therapies and subsequently developed a DFS event and 2 patients who received new anti-cancer therapies and did not develop a DFS event. The sensitivity analysis censoring patients with two or more missed consecutive assessments at time of last adequate assessment showed a HR of 0.27 (95% CI: 0.15, 0.48) in the ITT population. Based on the low frequency of events impacted by this censoring rule and the results of the sensitivity analyses, FDA determined that not censoring patients for new anti-cancer therapy likely had minimal impact on the interpretation of results of the primary endpoint.

3. For patients who were determined to be ALK-positive by a locally performed ALK test, mandatory pre-treatment tumor samples were collected for retrospective confirmatory central ALK testing by the Ventana ALK IHC assay. According to the clinical study report (CSR) for ALINA, retrospective central testing for ALK status could not be performed for 15 patients who were enrolled based on a local ALK test result. Thirteen of the 15 patients are not tested due to missing samples, 1 patient (Patient ID: (b) (6)) was not centrally tested due to lack of a suitable sample for analysis, and 1 patient (Patient ID: (b) (6)) had a failed central test ("due to detached tissues"). Of these 15 patients, 7 patients elected to withdraw from the trial prior to receiving any treatment and 8 patients enrolled and were treated on the trial. As part of a response to an information request, the Applicant conducted sensitivity analyses of DFS as assessed by investigator in the subset of patients with stage IB-IIIA and stage II-IIIA disease while excluding the 15 patients. The results are consistent with that of the primary analysis results in both patient populations, with a HR of 0.23 (95% CI 0.13 - 0.42) in the stage IB-IIIA population and a HR of 0.24 (95% CI 0.13 - 0.44) in the stage II-IIIA population.

4. Tumor stage (stage IB vs. II vs. IIIA) and race (Asian vs. Non-Asian) were two stratification factors in ALINA. There were some differences between the assigned values of the categories of the stratification factor tumor stage by randomization via the Interactive Web Response System (IWRS) and the electronic case report form (eCRF) as presented below in the ITT population.

Table 16 FDA – The Concordance of Tumor Stage as reported in IWRS vs. eCRF

		Tumor Stage, IWRS			Total
Tumor Stage, eCRF		IB	II	IIIA	
	IB	20	5	1	26
	II	4	84	2	90
	IIIA	2	3	136	141
	Total	26	92	139	257

Source: FDA analyses of the Applicant submitted data ADTTE. DCO: June 26, 2023.

FDA analysis of the primary endpoint of investigator-assessed DFS, stratified by tumor stage per eCRF and race resulted in a DFS HR of 0.24 (95% CI: 0.14, 0.43) in the ITT population, indicating that, in general, the impact of stratification error on the interpretation of DFS results is minimal.

5. The pre-specified sensitivity analysis censoring patients from enrollment sites in Russia and Ukraine on February 24, 2022, resulted in a DFS HR of 0.25 (95% CI: 0.14, 0.45) in the ITT population, indicating that, in general, the impact of administrative censoring in these sites on the interpretation of DFS results is likely minimal.

6. FDA considers landmark analyses of DFS exploratory only and notes these results should be interpretated with caution.

7. For OS results, refer to *Efficacy Results – Secondary and other relevant endpoints section* below.

Data Quality and Integrity

The Applicant's Position: No issues were identified with the data quality or integrity from ALINA which could affect the efficacy results. Information requested by the Office of Scientific Investigations (OSI) for Study ALINA is provided in Module 5.3.5.4.

The FDA's Assessment:
FDA generally agrees with the Applicant's position with regards to data quality and integrity. While minor issues were identified during inspections of clinical sites and the Applicant, these issues were considered unlikely to significantly affect the overall reliability of the efficacy data

generated in the ALINA trial (see Section 4.1 for more details).

Efficacy Results – Secondary and other relevant endpoints

Data: At the CCOD, the OS data were immature with low event-to-patient ratio (alectinib arm: 2/130 deaths; chemotherapy arm: 4/127 deaths) in the ITT population. There was an additional death in the chemotherapy arm where only the year was reported. This event was censored at the last date the patient was known to be alive.

At the CCOD, the exploratory endpoint CNS-DFS in the ITT population showed clinically meaningful prolongation of CNS-DFS with alectinib compared to chemotherapy. A higher proportion of patients in the chemotherapy arm (14.2%) had experienced CNS recurrence or death compared to the alectinib arm (3.8%), with a stratified HR of 0.22 (95% CI: 0.08, 0.58). A higher proportion of patients were alive and disease-free in CNS in the alectinib arm compared to the chemotherapy arm at 2 years (98.4% vs. 85.8%, respectively), and at 3 years (95.5% vs. 79.7%, respectively).

The Applicant's Position: The secondary endpoint of OS in the ITT population was immature with low event-to-patient ratio. The exploratory end point CNS-DFS in the ITT population showed clinically meaningful prolongation of CNS-DFS in the alectinib arm compared to the chemotherapy arm.

The FDA's Assessment:

OS was a pre-specified secondary endpoint in ALINA. FDA agrees with the Applicant's description of the OS results.

Time to CNS recurrence or death was defined as the time from randomization to the first documented recurrence of disease in the CNS or death from any cause, whichever occurs first. Patients who are not reported as experiencing disease recurrence in the CNS or death are censored at the date of the last disease assessment. Patients who experienced non-CNS recurrence prior to a CNS recurrence are censored at the date of non-CNS recurrence. The CNS recurrence was 14% (18/127; 14 CNS disease recurrence and 4 deaths) in the chemotherapy arm and 4% (5/130; 4 CNS disease recurrence and 1 death) in the alectinib arm.

In patients with ALK-positive NSCLC, disease recurrence in the brain occurs in up to 60% of patients during their disease course (Zhang et al., 2015). While FDA considers time to CNS recurrence or death as descriptive only, and results should be interpreted with caution because of confounding of CNS-DFS by systemic recurrences, alectinib appears to decrease the risk of CNS recurrence, which is important given the morbidity and mortality associated with CNS metastases.

Dose/Dose Response

The Applicant's Position: Refer to section 6.2.2.1 and 19.4.2.

The FDA's Assessment:
FDA agrees with the Applicant's position.

Durability of Response

The Applicant's Position: The number patients with a DFS event in the alectinib arm is very low in the ITT population (15 events). This low rate of events reflects that the majority of patients are still alive and disease free. The 2-year DFS data provides evidence that efficacy from alectinib in this population is durable.

The FDA's Assessment:

FDA agrees with the Applicant's description of the results of investigator-assessed DFS.

Persistence of Effect

The Applicant's Position: The 3-year DFS data showed a clinical meaningful improvement with adjuvant alectinib treatment compared to chemotherapy, which indicates the persistence of treatment effect of adjuvant alectinib after the completion of 2-year treatment. However, the results should be interpreted with caution considering the data beyond 27.8 months were immature, thus no definitive claims can be made.

The FDA's Assessment:

FDA agrees with the Applicant's description of persistence of effect of alectinib. Longer term follow-up will be needed to better characterize this persistence of effect after completion of 2 years of treatment.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data: Completion rates for the exploratory endpoint, the Short Form 36-item health survey, version 2 (SF-36v2), were high at baseline, 96.9% vs. 94.5% for the alectinib and chemotherapy arms, respectively, and remained high throughout the study at the time of CCOD. For the alectinib arm, the mean scores for 5 of the 8 health domains and the mental component summary (MCS) met or exceeded the minimal important difference (MID) for within-group change by Week 12 and were maintained to Week 96; the MID was also met or exceeded for a sixth health domain and the Physical Component Summary (PCS) by Week 96. Overall, there was no evidence of detrimental impact on health-related quality of life (HRQoL) over the 96 weeks of treatment with alectinib.

During treatment with chemotherapy, a negative MID was exceeded for 2 health domains; while in the off-treatment period, a positive MID was met or exceeded for 5 of the 8 health domains, MCS and PCS. Overall, during treatment with chemotherapy, mean scores tended to be lower compared to their respective mean scores during the off-treatment Disease Follow-Up period.

The Applicant's Position: Overall, there was no evidence of detrimental impact on HRQoL over the 96 weeks of treatment with alectinib, as assessed by the exploratory patient-reported

endpoint the SF-36v2.

The FDA's Assessment:

Mean change from baseline in physical component summary (PCS), mental component summary (MCS), and physical function (PF) scale according to SF-36V2 were exploratory endpoints in ALINA. Patients randomized to the chemotherapy arm received up to 4 (21-day) cycles of treatment whereas patients randomized to the alectinib arm could continue to receive treatment up to Week 104. According to the Applicant submitted results, compliance rate for the SF-36V2 up to week 12 was at least 90% in both arms. FDA did not independently verify the compliance rates or the analyses of PRO endpoints. FDA considers PRO results presented in this section exploratory only as the analyses of these endpoints were not included under a formal testing plan to control the overall study-wise Type I error rate. Claims of detrimental impact (or lack thereof) from adjuvant therapy are a tolerability consideration and were not sufficiently measured using SF-36v2 alone. For example, an overall side effect impact item should have been used to assess tolerability.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position: Not applicable.

The FDA's Assessment:

FDA independently performed subgroup analyses based on selected patient characteristics in the ITT population, as presented in Table 17 below. While these subgroup analyses are considered exploratory, there are no obvious outliers.

Table 17 FDA – Investigator-assessed Disease-free Survival in selected subgroups

Characteristics	Alectinib (# of DFS events/N)	Chemotherapy (# of DFS events/N)	HR (95% CI)
Sex			
Female	8/75	22/59	0.22 (0.10, 0.50)
Male	7/55	28/68	0.26 (0.11, 0.60)
Age			
<65	11/103	32/93	0.26 (0.13, 0.52)
≥65	4/27	18/34	0.24 (0.08, 0.71)
≥75	1/3	2/3	0.24 (0.02, 2.67)
Race[1]			
White	6/55	26/52	0.17 (0.07, 0.41)
Black/African American	0/1	0	---
Asian	9/72	22/71	0.36 (0.17, 0.79)
Other/Unknown	0/2	2/4	---
History of tobacco use			
Never	10/84	27/70	0.27 (0.13, 0.55)
Former/Current	5/46	23/57	0.21 (0.08, 0.54)
Region[1,2]			
USA	0/2	0/1	---
Europe	6/45	18/35	0.19 (0.07, 0.47)
Asia	9/83	32/91	0.28 (0.13, 0.58)
Stage AJCC 7th ed.			
IB	1/17	3/9	0.28 (0.03, 2.81)
IIA	4/38	15/42	0.24 (0.08, 0.73)
IIB	1/5	3/5	0.23 (0.02, 2.24)
IIIA	9/70	29/71	0.24 (0.11, 0.51)
ECOG			
0	7/72	25/65	0.20 (0.09, 0.46)
1	8/58	25/62	0.31 (0.14, 0.69)

DCO: June 26, 2023; HR, Hazard ratio.
[1]Empty rows for hazard ratios are reported for no events in either treatment arm; [1,2]Egypt, Kazakhstan, Russia, and Turkey were included in Asia and all 3 patients from North America are from USA

FDA also conducted exploratory analyses of investigator-assessed DFS by stage as defined per AJCC 8th edition (Table 18). The results are consistent with the analyses of DFS by stage as defined per AJCC 7th edition (Table 17).

Table 18 FDA – Investigator-assessed Disease-free Survival by Stage per AJCC 8th edition

	Stage IB		Stage II		Stage IIIA		Stage IIIB	
AJCC 8th ed. (eCRF)	Alectinib (n=6)	Chemo (n=5)	Alectinib (n=51)	Chemo (n=48)	Alectinib (n=66)	Chemo (n=68)	Alectinib (n=7)	Chemo (n=6)
Median, mos (95% CI)[1]	NR (NE, NE)	NR (41.3, NE)	NR (42.3, NE)	NR (24.9, NE)	NR (NE, NE)	44.4 (23.5, NE)	NR (26.5, NE)	13.2 (3.0, NE)
HR (95% CI)[2]	<0.01 (0.00, NE)		0.28 (0.11, 0.70)		0.22 (0.10, 0.51)		0.16 (0.03, 0.85)	

[1] Using Kaplan-Meier method; [2] HR, Hazard ratio, using unstratified Cox regression model; NR, Not reached; NE, Not estimable; DCO: 06/26/2023; INV, Investigator; DCO: June 26, 2023.

An analysis of DFS by blinded independent central review (BICR) was performed for ALINA. BICR-assessed DFS results (Table 19) are consistent with the investigator-assessed DFS primary efficacy results.

Table 19 FDA – Efficacy results – disease-free survival (DFS) according to blinded independent central review (BICR)

	Alectinib N=116	Chemotherapy N=115
Disease-Free Survival (DFS), Stage II-IIIA		
Events (%)	13 (11%)	34 (30%)
Median, months (95% CI)[1]	NR (NE, NE)	NE (37.4, NE)
Hazard Ratio (95% CI)[2]	0.29 (0.15, 0.55)	
Disease-Free Survival (DFS), ITT		
N	130	127
Events (%)	16 (12%)	39 (31%)
Median, months (95% CI)[1]	NR (NE, NE)	NE (37.4, NE)
Hazard Ratio (95% CI)[2]	0.30 (0.17, 0.54)	

DCO date: June 26, 2023.
[1]Kaplan-Meier method; [2]Stratified Cox model stratified by race (Asian vs. other races) in Stage II-IIIA and stratified by race (Asian vs. other races) and tumor stage (Stage IB vs. II vs. IIIA) in ITT

Source: FDA analyses of the Applicant submitted data ADTTE

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

The demonstration of efficacy of alectinib for the proposed indication is based solely on the results of the ALINA trial (Study BO40336), in which 130 patients were randomized to receive alectinib and 127 patients were randomized to receive platinum-based chemotherapy in the adjuvant setting after resection of ALK-positive NSCLC. The results of the ALINA trial presented in this application are based on a pre-planned interim analysis that occurred after 59 DFS events (66% information fraction) were observed. The primary endpoint for ALINA is DFS by investigator assessment, which was hierarchically tested first in patients with stage II-IIIA disease, followed by DFS in the overall population of patients with stage IB-IIIA disease (ITT population). In both populations, there was a statistically significant and clinically meaningful improvement in DFS in patients randomized to receive alectinib compared to patients randomized to receive chemotherapy. For patients with stage II-IIIA disease, the HR for DFS was 0.24 (95%CI: 0.13, 0.45) with a p-value <0.0001 (with an alpha boundary for significance of 0.0118). For the overall population, the HR for DFS was 0.24 (95% CI: 0.13, 0.43), with a p-value of 0.0001 (with an alpha boundary for significance of 0.0077).

In exploratory subgroup analyses, DFS was consistent across stages of NSCLC per the 7th edition of the AJCC staging system. For patients with stage IB NSCLC, the DFS HR was 0.28 (95% CI: 0.03, 2.81); the interpretation of the DFS HR as well as the corresponding wide 95% CI should be interpreted with caution due to a small number of patients and the small number of events in this subgroup (1 DFS event in the alectinib arm and 3 events in chemotherapy arm). For patients with stage II NSCLC, the DFS HR was 0.24 (95% CI: 0.09, 0.65). For patients with stage IIIA NSCLC, the DFS HR was 0.24 (95% CI: 0.11, 0.51). A consistent DFS treatment effect across stages supports the finding of improved DFS with alectinib compared to chemotherapy in the overall population (i.e., patients with stage IB – IIIA NSCLC). The DFS benefit observed in the overall population does not appear to be driven by patients with a specific stage of NSCLC. See Section 8.1.2 of the Assessment Aid for additional details.

8.1.4. Assessment of Efficacy Across Trials

The Applicant's Position: Not applicable as efficacy data in the submitted dossier is based on a single, pivotal Phase III study.

The FDA's Assessment:

FDA agrees. The efficacy data were based solely on the results of the ALINA trial.

8.1.5. Integrated Assessment of Effectiveness

The Applicant's Position: Not applicable as efficacy data in the submitted dossier is based on a single, pivotal Phase III study.

The FDA's Assessment:
The efficacy of alectinib for the adjuvant treatment of patients with ALK-positive NSCLC following complete tumor resection is based on a pre-planned interim analysis of DFS in the ALINA trial that occurred when 66% of the total pre-specified DFS events at the planned final analysis in patients with stage II-IIIA NSCLC had occurred. FDA agrees that alectinib as adjuvant treatment following complete tumor resection for patients with ALK-positive NSCLC demonstrated a statistically significant and clinically meaningful reduction in DFS for patients with stage II-IIIA disease and for the overall population of patients with stage IB-IIIA disease. In the stage II-IIIA population, the median DFS was NR (95% CI: NE, NE) in the alectinib arm and 44.4 months (95% CI: 27.8, NE) in the chemotherapy arm, with a HR of 0.24 (95% CI: 0.13, 0.45; p-value < 0.0001 with alpha boundary 0.0118) favoring alectinib. In the ITT population, the median DFS was NR (95% CI: NE, NE) in the alectinib arm and 41.3 months (95% CI: 28.5, NE) in the chemotherapy arm, with a HR of 0.24 (95% CI: 0.13, 0.43; p-value < 0.0001 with alpha boundary 0.0077). OS data are limited at the time of the data cutoff date, with 6 OS events in the ITT population. The statistical review did not identify any major issues (see Section 8.3 for further details).

One limitation of the results at this interim analysis for DFS is that the median DFS was not reached for the alectinib arm. No further statistical testing of DFS is planned, although a descriptive analysis will be performed at 89 DFS events in patients with stage II-IIIA NSCLC (the pre-specified final number of events). To better quantify median DFS and long-term outcomes (including the characterization of the persistence of effect of alectinib once patients have completed 2 years of treatment), a post-marketing commitment (PMC) will be issued for the Applicant to provide an updated descriptive DFS analysis at the pre-specified final number of events or when all patients have been followed for 5 years. In addition, OS was not planned to be formally tested, but exploratory analyses of OS are to be conducted at the time of the final DFS analysis and approximately 5 years after the last patient is enrolled. The PMC will also include a request for submission of results for these descriptive OS analyses. Please see Section 13 of the Assessment Aid for additional details.

As there are no remaining formal analyses pending, it is unlikely that there will be any additional interpretable statistical inference from the remaining analyses of this trial.

8.2. Review of Safety

The Applicant's Description: The safety review for this sNDA of alectinib 600 mg BID as adjuvant therapy in patients with resected Stage IB-IIIA ALK-positive NSCLC, is primarily based on results

from the ALINA study (CCOD: 26 June 2023; adjuvant population; ALINA CSR). Safety results from ALINA are discussed in Sections 8.2.4- 8.2.9

In addition, pooled safety data are provided as part of the comprehensive safety evaluation to contextualize the safety data from the adjuvant setting. The pooled mNSCLC population comprises safety data from the three studies (BO28984 [CCOD: 29 November 2019], NP28761 [CCOD: 12 October 2017], NP28673 [CCOD: 27 October 2017]) that formed the basis of approval of alectinib as a treatment for ALK-positive NSCLC in the locally advanced and metastatic setting and is presented in the Module 5.3.5.3. ISS. Further, a comparison and overall pooling of the safety data from the adjuvant NSCLC setting from ALINA and the pooled mNSCLC data is provided in Section 8.2.11 and Module 2.7.4 SCS.

The Applicant's Position: Alectinib was generally well tolerated and manageable in patients with Stage IB–IIIA ALK-positive NSCLC after surgical resection. The safety results of alectinib observed in ALINA were generally consistent with the safety profile established in the mNSCLC clinical studies.

The FDA's Assessment:

FDA agrees that the safety review primarily focuses on the ALINA study (n=128) with additional supportive data provided from previous studies evaluating alectinib as treatment in the metastatic setting (Study BO28984 [ALEX, n=152] in the first-line setting and Studies NP28761 and NP28673 [n=253] in the second line setting; n=405 across studies in metastatic setting ["metastatic pooled safety dataset"]). The safety review includes evaluation of patients from these studies who received alectinib at the recommended dose of 600 mg BID (n=533; "overall pooled safety dataset"). ALINA is the only trial included in the safety dataset evaluating alectinib in the adjuvant setting.

8.2.1. Safety Review Approach

The Applicant's Position: The safety and tolerability assessment for ALINA was based on the frequency and nature of deaths (including due to AE), adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, AEs leading to dose modification, Selected AEs (defined based on the known safety profile of alectinib), clinical laboratory assessments, and vital sign measurements.

The FDA's Assessment:
FDA agrees with the Applicant's position regarding the safety review approach.

8.2.2. Review of the Safety Database

The Applicant's Description: The clinical safety data is presented as per the agreement with the Agency in the 17 January 2023 Type C Content and Format (IND 111723; Reference ID: 5109217):

Table 20 Applicant - Safety Population, Size, and Denominators

Safety Database for the Study Drug Individuals exposed to the study drug in this development program for the indication under review (N is the sum of all available numbers from the columns below)		
	Adjuvant NSCLC (ALINA Study)	
Clinical Trial Groups	Alectinib	Chemotherapy
Controlled trials conducted for this indication	N=128	N=120
All other than controlled trials conducted for this indication	0	0
Controlled trials conducted for other indications	0	0

Safety datasets have also been provided for the pooled safety data from the three studies (BO28984 [CCOD: 29 November 2019], NP28761 [CCOD:12 October 2017], NP28673 [CCOD: 27 October 2017]) that previously formed the basis of approval of alectinib as a treatment for ALK-positive NSCLC in the locally advanced and metastatic setting.

The FDA's Assessment:

FDA agrees with the Applicant's position regarding the safety datasets. In addition to the 128 patients who received alectinib on the ALINA trial, 405 patients who received alectinib on trial in the metastatic setting are included in the overall pooled safety data, as indicated above.

Overall Exposure

Data:

Table 21 Applicant - Study Treatment Exposure (Alectinib)

	Alectinib (N=128)
Treatment duration (months)	
n	128
Mean (SD)	21.3 (6.3)
Median	23.9
Min - Max	0 - 25
Dose intensity (%)	
n	128
Mean (SD)	91.1 (14.8)
Median	99.4
Min - Max	47 - 100
Number of doses	
n	128
Mean (SD)	1274.4 (380.7)
Median	1434.0
Min - Max	14 - 1522
Total cumulative dose (mg)	
n	128
Mean (SD)	711029.30 (243018.85)
Median	834300.00
Min - Max	8400.0 - 913200.0

Source: t_ex_SE_26JUN2023_40336

Table 22 Applicant - Exposure to Chemotherapy (ALINA Safety-Evaluable Population)

	Cisplatin- containing regimen n=119	Carboplatin- containing regimen n=14	Gemcitabine/Pemetrexed /Vinorelbine n=120
Treatment Duration (months)			
Mean (SD)	2.0 (0.7)	1.0 (0.6)	2.2 (0.5)
Median	2.1	0.7	2.1
Min-Max	0-4	0-2	0-4
Dose intensity (%)			
Median	100	100	100
Min-Max	86-101	83-100	91-101
Number of cycles			
Mean (SD)	3.6 (0.9)	2.3 (0.8)	3.8 (0.5)
Median	4.0	2.0	4.0
Min-Max	1-4	1-4	1-4

Source : t_ex_chemo_SE_26JUN2023_40336
Treatment duration is the date of the last study drug administration minus the date of the first study drug administration plus one day.
Dose intensity is the amount of study drug actually received divided by the expected amount to the time of the last administered dose.

The Applicant's Position: The median duration of exposure in the alectinib arm of ALINA (23.9 months; range: 0 – 25 months) was longer compared with the chemotherapy arm (2.1 months; range: 0 – 4 months). Consequently, in the ALINA Study, the AE reporting period was also longer for patients treated with alectinib with a maximum of 25 months compared to 4 months for patients treated with chemotherapy.

The FDA's Assessment:
FDA agrees with the Applicant's position.

An FDA analysis of adverse events (AEs) occurring in ≥ 10% of patients on the alectinib arm by duration of exposure showed that the incidence several adverse events were increased in patients with longer durations of exposure to alectinib, including hepatotoxicity, COVID-19, fatigue, increased weight, and bradycardia. However, the results of this analysis should be interpreted with caution given the small numbers of patients who had durations of exposure to alectinib less than 12 months and greater than or equal to 24 months. Although alectinib was to be administered for up to only 24 months, some patients may have had a longer duration of exposure over time due to treatment interruptions. The results of this analysis are shown in the table below:

Table 23 FDA – Adverse Events Occurring in ≥ 10% of Patients on the Alectinib Arm of ALINA by Duration of Exposure

Treatment Emergent Adverse Events ≥ 10% (Grades 1-4)	Alectinib N=128		
Months of Exposure	0 - <12 n=12 %	≥12 - <24 n=98 %	≥24 n=18 %
Hepatotoxicity	33	65	56
Constipation	33	43	44
Myalgia	17	38	28
COVID-19	0	33	28
Fatigue	17	21	50
Rash	8	26	22
Cough	17	21	11
Edema	8	19	0
Renal impairment	17	17	11
Increased weight	0	15	11
Abdominal pain	8	12	17
Diarrhea	17	10	22
Dysgeusia	8	13	17
Dyspnea	25	11	11
Bradycardia	0	13	11
Headache	0	13	6

Source: FDA analyses of the Applicant submitted data ADSL and ADAE; DCO: June 26, 2023.

Relevant characteristics of the safety population:

Data: Refer to Section 8.1.2/Table of Demographic Characteristics for the summary of demographics and baseline characteristics of the alectinib and chemotherapy arms from ALINA in the ITT population and Section 8.1.1 Trial design for an overview of the exclusion criteria.

The study population was generally balanced between male patients (47.9%) and female patients (52.1%), with a median patient age of 56.0 years (range: 26-87 years). Most patients

(76.3%) were <65 years of age. All patients had a baseline ECOG performance status (PS) of 0 (53.3% overall) or 1 (46.7% overall), and most were never smokers (59.9%).

The Applicant's Position: The demographics and baseline characteristics were generally well balanced between the alectinib and chemotherapy arms in the ITT population.

The FDA's Assessment:
FDA agrees that the study arms for the safety population are generally balanced based on demographics and stratification factors, except for differences between arms for sex and tobacco use history as described in Section 8.1.2 (Study Results).

Adequacy of the safety database:

The Applicant's Position: The safety profile of alectinib as observed in a total of 128 patients in ALINA study, is generally consistent with that of alectinib in the mNSCLC population (n=405). Therefore, the Applicant considers that the size of the database is adequate to support the safety of alectinib 600 mg BID in patients with ALK-positive NSCLC after surgical resection and to support the benefit-risk assessment of the proposed indication.

The FDA's Assessment:
FDA agrees that the safety profile observed for patients on the ALINA trial is generally consistent with the safety profile observed for the patients in the metastatic NSCLC population. However, incidence rates for certain toxicities were different between patients treated with alectinib on ALINA versus patients treated with alectinib in the metastatic NSCLC setting, including hepatotoxicity and CPK elevations (see Section 8.2.5 of the Assessment Aid for further details). FDA agrees that the overall pooled safety dataset provides evidence to support the benefit/risk assessment for use in the adjuvant setting.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position: No issues relating to data integrity or quality were identified for the studies included in this submission.

The FDA's Assessment:
In general, FDA agrees that there are no issues related to the integrity of data; however, some minor discrepancies in AE reporting at two clinical sites, as well as minor documentation issues for the Applicant, were reported during the site and Applicant investigations as discussed in Section 4.1 (Office of Scientific Investigations) of the Assessment Aid. Based on FDA's assessment these issues do not significantly affect the overall reliability of the safety data generated by the ALINA trial.

Categorization of Adverse Event

The Applicant's Position: All adverse events were collected as specified in the ALINA Protocol BO40336 (Version 7) and analyzed as specified in the SAP v2. All verbatim adverse event terms (including treatment-emergent AEs) were mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms (Version 26). Adverse event severity values were graded according to NCI CTCAE v5. Investigators assessed causality, seriousness, and severity of AEs. Multiple occurrences of the same event were counted once at the maximum grade. Relevant laboratory data were classified according to NCI CTCAE v5.0 for and summary tables of shifts from baseline to the worst post-baseline value are presented by treatment arm.

Selected AEs were defined using Standardized MedDRA queries (SMQs), where applicable. If no SMQs were available, MedDRA System Organ Class (SOC), High Level Terms (HLT), High Level Group Terms (HLGT), Roche Standard MedDRA Adverse Event Grouped Terms (AEGTs), or Preferred Terms (PTs) were used, as listed in the table below:

Table 24 Applicant - Selected AEs Search Criteria

Selected AE	Search Criteria
Abnormal Renal Function	Combination of MedDRA SMQ Acute Renal Failure narrow, and MedDRA SOC Renal and Urinary Disorders, and MedDRA High Level Group Term Renal and Urinary Tract Investigations and Urinalyses
Gastrointestinal Tract Adverse Events	MedDRA SOC Gastrointestinal Disorders
Hematologic Abnormalities	MedDRA SMQ Haematopoietic Cytopenias wide
Hepatocellular or Cholestatic Damage AEs or Abnormal Liver Function Tests	MedDRA SMQ Drug Related Hepatic Disorders - Comprehensive Search narrow
Interstitial Lung Disease and Pneumonitis	MedDRA SMQ Interstitial lung Disease narrow
Muscular Adverse Events, Creatine Phosphokinase Elevations	MedDRA High Level Group Terms of 'Musculoskeletal and Connective Tissue Disorders NEC', 'Enzyme Investigations NEC' and 'Muscle Disorders'
Skin Disorders	MedDRA SOC Skin and Subcutaneous Tissue Disorders
Vision Disorders	MedDRA SOC Eye Disorders
Bradycardia	PT Bradycardia and PT Sinus bradycardia
Dysgeusia	PT Dysgeusia, PT Hypogeusia, PT Taste disorder
Edema	PT Oedema, Oedema Peripheral, Generalised Oedema, Eyelid Oedema, Periorbital Oedema, Face Oedema, Localised Oedema, Lip swelling, Peripheral swelling, Swelling, Swelling face, Joint swelling, Swelling of eyelid

The FDA's Assessment:

FDA agrees with categorization of AEs. The FDA review was completed using MedDRA (version 26) PTs and NCI-CTCAE (version 5.0) grade, as well as custom grouped terms (GTs), when performing independent analyses of AEs.

For purposes of the FDA review of safety, incidences of AEs were generally analyzed without consideration of relatedness to investigational product; additionally, as there

may be heterogeneity between investigators and difficulty in accurately assigning attribution of AEs to study therapy, FDA generally reports treatment-emergent AEs rather than drug-related AEs.

Routine Clinical Tests

The Applicant's Description: The schedule of assessments for ALINA is provided in Appendix 1 of the study protocol. Patients in both treatment arms underwent physical examination at screening and at baseline. Laboratory assessment, urinalysis, vital signs and ECOG performance status were measured at screening, baseline and at the safety follow-up visit in both arms. The duration of monitoring was longer in the alectinib arm compared to the chemotherapy arm, with assessments scheduled every three weeks (Weeks 1-12), every six weeks (Weeks 13-48) and every 12 weeks (Weeks 49-96), while the chemotherapy arm maintained a three-week assessment during Weeks 1-12. Pregnancy testing was performed for both arms at screening and at all scheduled safety visits and as clinically indicated. ECGs were conducted at screening, baseline, at Weeks 3, 24, 60 and at the safety follow up visit in the alectinib arm. In the chemotherapy arm, ECGs were performed at screening, baseline, week 3 and at the safety follow up visit.

The FDA's Assessment:
FDA agrees with the Applicant's position.

8.2.4. Safety Results

The Applicant's Description: ALINA study results are presented in this section. While evaluating the safety data, it is important to note that the median duration of treatment was significantly different between the two arms (23.9 months in the alectinib arm vs. 2.1 months in the chemotherapy arm). As all AEs were reported during treatment and until 28 days after last dose of alectinib or 28 days after the end of the last cycle of chemotherapy (i.e., a maximum of 25 months for patients randomized to the alectinib arm and 4 months for patients randomized to the chemotherapy arm), the period in which AEs were collected for the alectinib arm was substantially longer than the chemotherapy arm.

The FDA's Assessment:
FDA agrees with the Applicant's description regarding the difference in duration of treatment and monitoring and reporting of AEs between the treatment arms.

Deaths

Data: A total of 2 patients (1.6%) in the alectinib arm and 5 patients (4.2%) in the chemotherapy arm died. All deaths occurred during the follow-up period (off-treatment). There were no Grade 5 AEs. In the alectinib arm, both patients died due to disease recurrence; 1 patient (in the alectinib arm) died within ≤30 days of last study drug administration. The causes of death for the 5 patients who died in the chemotherapy arm were disease recurrence (2 patients), bilateral pneumonia (1 patient), COVID-19 (1 patient), and unknown (1 patient).

The Applicant's Position: At the CCOD, fewer deaths had occurred in the alectinib arm compared to the chemotherapy arm. There was no pattern or trend in the cause of deaths.

The FDA's Assessment:

FDA agrees that the deaths observed in the ALINA study do not raise safety concerns. All deaths in both study arms occurred while off-treatment and, as such, there were no grade 5 AEs. Both deaths on the alectinib arm were due to disease recurrence.

Serious Adverse Events

Data: The proportion of patients who experienced at least one SAE was 13.3% in the alectinib arm and 8.3% in the chemotherapy arm. Most of these SAEs were Grade 3 or less in severity and had resolved by the CCOD. Two patients in the alectinib arm experienced two Grade 4 SAEs reported as acute myocardial infarction (preferred term[PT]) and uterine prolapse (PT). The proportion of patients who discontinued treatment due to an SAE was 0.8% (1 patient, pneumonitis [PT]) in the alectinib arm and 3.3% (4 patients) in the chemotherapy arm. The proportion of patients who required treatment dose reductions or interruptions due to an SAE was 5.5% in the alectinib arm and 3.3% the chemotherapy arm. SAEs by SOC and PT are summarized in Table 25 below.

Table 25 Applicant - Serious Adverse Events

MedDRA System Organ Class MedRA Preferred Term	Alectinib (N=128)	Chemotherapy (N=120)
Total number of patients with at least one adverse event	17 (13.3%)	10 (8.3%)
Overall total number of events	20	16
Infections and infestations		
Total number of patients with at least one adverse event	11 (8.6%)	2 (1.7%)
Total number of events	11	2
Appendicitis	4 (3.1%)	0
Pneumonia	3 (2.3%)	1 (0.8%)
Influenza	1 (0.8%)	0
Lower respiratory tract infection	1 (0.8%)	0
Pneumonia viral	1 (0.8%)	0
Urinary tract infection	0	1 (0.8%)
Urosepsis	1 (0.8%)	0
Gastrointestinal disorders		
Total number of patients with at least one adverse event	2 (1.6%)	4 (3.3%)
Total number of events	2	8
Nausea	0	2 (1.7%)
Abdominal pain	0	1 (0.8%)
Colitis	0	1 (0.8%)
Epigastric discomfort	0	1 (0.8%)
Gastritis erosive	1 (0.8%)	0
Ileus paralytic	1 (0.8%)	0
Pancreatitis acute	0	1 (0.8%)
Regurgitation	0	1 (0.8%)
Vomiting	0	1 (0.8%)
Respiratory, thoracic and mediastinal disorders		
Total number of patients with at least one adverse event	2 (1.6%)	1 (0.8%)
Total number of events	2	1
Dyspnoea	1 (0.8%)	0
Pneumonitis	1 (0.8%)	0
Pulmonary embolism	0	1 (0.8%)
Cardiac disorders		
Total number of patients with at least one adverse event	2 (1.6%)	0
Total number of events	2	0
Acute myocardial infarction	2 (1.6%)	0
Investigations		
Total number of patients with at least one adverse event	0	2 (1.7%)

Total number of events	0	2
Neutrophil count decreased	0	2 (1.7%)
Reproductive system and breast disorders		
Total number of patients with at least one adverse event	2 (1.6%)	0
Total number of events	2	0
Benign prostatic hyperplasia	1 (0.8%)	0
Uterine prolapse	1 (0.8%)	0
Blood and lymphatic system disorders		
Total number of patients with at least one adverse event	0	1 (0.8%)
Total number of events	0	1
Febrile neutropenia	0	1 (0.8%)
General disorders and administration site conditions		
Total number of patients with at least one adverse event	0	1 (0.8%)
Total number of events	0	1
Fatigue	0	1 (0.8%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Total number of patients with at least one adverse event	1 (0.8%)	0
Total number of events	1	0
Bladder cancer	1 (0.8%)	0
Vascular disorders		
Total number of patients with at least one adverse event	0	1 (0.8%)
Total number of events	0	1
Embolism	0	1 (0.8%)

Source: t_ae_SER_SE_26JUN2023_40336

The Applicant's Position: The nature and incidence of SAEs observed was generally consistent with the known safety profiles of alectinib and chemotherapy, respectively or the underlying disease. Most SAEs were Grade 3 or less in severity and had resolved by the CCOD. The frequency of treatment discontinuations or dose modifications due to SAEs in the alectinib arm was low, showing a good tolerability profile of alectinib and patient adherence to treatment, despite the longer treatment duration of alectinib compared to chemotherapy.

The FDA's Assessment:

FDA evaluated serious adverse events (SAEs) based on grouped terms. FDA agrees that the nature and incidence of SAEs were generally consistent with the known safety profiles of alectinib and chemotherapy. SAEs occurred in 13% of patients treated with alectinib and 8% of patients treated with chemotherapy in ALINA. In patients treated with alectinib, SAEs occurring in ≥1% of patients were pneumonia (3.9%), appendicitis (3.1%), and acute myocardial infarction (1.6%). In the chemotherapy group, SAEs occurring in ≥1% of patients were abdominal pain, nausea, and neutropenia (1.7% each).

Dropouts and/or Discontinuations Due to Adverse Effects

Data: The proportion of patients who experienced at least one AE leading to treatment discontinuation in the alectinib arm (5.5%) was lower than in the chemotherapy arm (12.5%).

The most frequent AEs by PT leading to treatment discontinuations in the alectinib arm were pneumonitis (2.3%) and blood creatinine increased (0.8%). The most frequent AEs by PT leading to treatment discontinuations in the chemotherapy arm were nausea (3.3%), asthenia (2.5%) and blood creatinine increased, fatigue, vomiting, and tinnitus (1.7% each).

The Applicant's Position: Overall, alectinib was generally well tolerated as evidenced by the lower rates of discontinuation.

The FDA's Assessment:
FDA evaluated treatment discontinuations due to adverse events (AEs) based on grouped terms. FDA agrees that alectinib was generally well tolerated based on rates of treatment discontinuation. Treatment discontinuation due to AEs occurred in 5% of patients treated with alectinib and 13% of patients treated with chemotherapy in ALINA. In patients treated with alectinib, treatment discontinuations due to AEs occurring in ≥1% of patients were pneumonitis (2.3%) and hepatotoxicity (1.6%), while in patients treated with chemotherapy, treatment discontinuations due to AEs occurring in ≥1% of patients were renal impairment and fatigue (4.2% each), nausea (3.3%), and tinnitus and vomiting (1.7% each).

Dose Interruption/Reduction Due to Adverse Effects

Data: The proportion of patients who experienced AEs leading to study treatment interruption in the alectinib arm (27.3%) was higher than in the chemotherapy arm (18.3%). The most frequent AEs by PT that led to study treatment interruption in the alectinib arm were ALT increased and blood creatine phosphokinase (CPK) increased (5.5%, each), AST increased (4.7%), COVID-19 (4.7%), and blood bilirubin increased (3.9%). The most frequent AEs by PT that led to study treatment interruption in the chemotherapy arm by PT were neutrophil count decreased and neutropenia (5.0%, each), and COVID-19 (0.8%).

The proportion of patients who experienced at least one AE leading to study treatment dose reduction in the alectinib arm (25.8%) was higher than in the chemotherapy arm (10.0%). The most frequent AEs by PT that led to study treatment dose reduction in the alectinib arm were blood CPK increased (6.3%) and blood bilirubin increased (3.9%). The most frequent AE by PT that led to study treatment dose reduction in the chemotherapy arm was nausea (3.3%).

The Applicant's Position: Overall, alectinib was generally well tolerated. In general, most adverse events were recognized and managed appropriately by the treating physician with dose modifications per protocol specified criteria.

The FDA's Assessment:
FDA evaluated dose interruptions and reductions due to AEs based on grouped terms. FDA agrees that alectinib was generally well tolerated based on rates of dose interruptions and reductions and that the AEs leading to these dose modifications are generally reflective of alectinib's known safety profile.

Dose interruptions due to AEs occurred in 27% of patients in the alectinib arm and 18% of patients in the chemotherapy arm of ALINA. Among the patients treated with alectinib, dose interruptions due to AEs occurring in ≥2% of patients were hepatotoxicity (9%), increased blood creatinine phosphokinase (CPK; 5%), COVID-19 (4.7%), and abdominal pain, myalgia, and pneumonia (2.3% each). In the chemotherapy group, dose interruptions due to AEs occurring in ≥2% of patients were neutropenia (10%) and leukopenia (4.2%).

Dose reductions due to AEs occurred in 26% of patients in the alectinib arm and 10% of patients in the chemotherapy arm of ALINA. In the alectinib group, dose reductions due to AEs occurring in ≥2% of patients were hepatotoxicity and increased blood CPK (6% each), rash (3.1%), and bradycardia and myalgia (2.3% each). Among patients treated with chemotherapy, dose reductions due to AEs occurring in ≥2% of patients were neutropenia (5%), leukopenia and nausea (3.3% each), and vomiting (2.5%).

Significant Adverse Events

Selected Adverse Events

Data: The selected AEs presented in the analysis were defined based on the safety profile of alectinib and were closely monitored during the study. The majority of patients reported at least one selected AE (94.5% in the alectinib arm and 89.2% in the chemotherapy arm).

The proportion of patients who experienced at least one Grade 3-5 selected AE (17.2% vs 27.5%), serious selected AE (2.3% vs. 5.8%), selected AE leading to treatment discontinuation (4.7% vs.8.3%) were lower in the alectinib arm compared to the chemotherapy arm. No patients experienced Grade 5 selected AEs and one patient experienced a Grade 4 selected AE of blood CPK increased in the alectinib arm.

The proportion of patients who experienced selected AEs leading to treatment dose reduction or interruption was 36.7% in the alectinib arm and 20.0% in the chemotherapy arm. The incidence and nature of the selected AEs are summarized in Table 26 below.

Table 26 Applicant - Selected Adverse Events by Preferred Term, Safety-Evaluable Patients

	Alectinib (N=128)					Chemotherapy (N=120)				
Selected Adverse Events	All Grades	Grade 3/4/5	Serious	Leading to Treatment Discontinuation	Leading to Treatment Dose Reduction or Interruption	All Grades	Grade 3/4/5	Serious	Leading to Treatment Discontinuation	Leading to Treatment Dose Reduction or Interruption
Total number of patients with at least one adverse event	121 (94.5%)	22 (17.2%)	3 (2.3%)	6 (4.7%)	47 (36.7%)	107 (89.2%)	33 (27.5%)	7 (5.8%)	10 (8.3%)	24 (20.0%)
Gastrointestinal Tract Adverse Events	87 (68.0%)	4 (3.1%)	2 (1.6%)	0	9 (7.0%)	95 (79.2%)	9 (7.5%)	4 (3.3%)	4 (3.3%)	7 (5.8%)
Hematologic Abnormalities	34 (26.6%)	1 (0.8%)	0	0	1 (0.8%)	56 (46.7%)	25 (20.8%)	3 (2.5%)	2 (1.7%)	19 (15.8%)
Muscular Adverse Events, CPK Elevations	92 (71.9%)	8 (6.3%)	0	0	17 (13.3%)	12 (10.0%)	2 (1.7%)	0	0	0
Hepatocellular or Cholestatic Damage AEs or Abnormal Liver Function Tests	78 (60.9%)	6 (4.7%)	0	2 (1.6%)	18 (14.1%)	16 (13.3%)	0	0	0	0
Skin Disorders	50 (39.1%)	2 (1.6%)	0	0	6 (4.7%)	22 (18.3%)	0	0	0	0
Abnormal Renal Function	27 (21.1%)	1 (0.8%)	0	1 (0.8%)	3 (2.3%)	17 (14.2%)	0	0	5 (4.2%)	1 (0.8%)
Dysgeusia	17 (13.3%)	0	0	0	1 (0.8%)	4 (3.3%)	0	0	0	0
Oedema	20 (15.6%)	0	0	0	0	2 (1.7%)	0	0	0	0
Bradycardia	15 (11.7%)	0	0	0	3 (2.3%)	0	0	0	0	0
Vision Disorders	12 (9.4%)	0	0	0	0	3 (2.5%)	0	0	0	0
Interstitial Lung Disease	4 (3.1%)	1 (0.8%)	1 (0.8%)	3 (2.3%)	0	0	0	0	0	0

Source: t_ae_sel_SE_26JUN2023_40336

The Applicant's Position: The overall safety profile of alectinib was generally consistent with the known risks of alectinib. The majority of the selected AEs were Grade 1-2 and non-serious in nature. Most of these patients were able to continue treatment with alectinib.

The FDA's Assessment:
While FDA agrees that the overall safety profile of alectinib was generally consistent with the known risks of alectinib, FDA used grouped terms for the evaluation of AEs instead of only evaluating AEs by single preferred terms.

Grade ≥3 AEs occurred in 30% of patients treated in the alectinib arm and 31% of patients treated in the chemotherapy arm of ALINA. Grade ≥3 AEs occurring in ≥2% of patients treated with alectinib were increased blood CPK (6%), hepatotoxicity (4.7%), and pneumonia and appendicitis (3.1% each), while those occurring in ≥2% of patients treated with chemotherapy were neutropenia (18%) and fatigue, leukopenia, and nausea (4.2% each).

Treatment Emergent Adverse Events and Adverse Reactions

Data: The proportion of patients who experienced at least one AE in the alectinib arm (98.4%) was comparable to the chemotherapy arm (93.3%).

Most patients reported low severity (Grade 1 or 2) AEs. The proportion of patients who experienced at least one Grade 3-5 AE in the alectinib arm (29.7%) was comparable to the chemotherapy arm (30.8%). No Grade 5 AEs were reported.

The proportion of patients who experienced at least one SAE was 13.3% in the alectinib arm and 8.3% in the chemotherapy arm.

There was a lower frequency of AEs leading to treatment discontinuation in the alectinib arm (5.5%) compared with the chemotherapy arm (12.5%). The proportion of patients who experienced at least one AE leading to treatment dose reduction or interruption in the alectinib arm (25.8% and 27.3%, respectively) was higher than in the chemotherapy arm (10.0% and 18.3%, respectively). An overview of key safety results is provided in Table 27.

Table 27 Applicant - Overview of Adverse Events, Safety-Evaluable Patients

	Alectinib (N=128)	Chemotherapy (N=120)
Total number of patients with at least one AE	126 (98.4%)	112 (93.3%)
Total number of AEs	1685	978
Total number of patients with at least one		
AE with fatal outcome (Grade 5)	0	0
Grade 3-5 AE	38 (29.7%)	37 (30.8%)
Serious AE	17 (13.3%)	10 (8.3%)
Serious AE leading to withdrawal from treatment	1 (0.8%)	4 (3.3%)
Serious AE leading to dose modification/interruption	7 (5.5%)	4 (3.3%)
Related Serious AE	2 (1.6%)	8 (6.7%)
AE leading to withdrawal from treatment	7 (5.5%)	15 (12.5%)
AE leading to dose modification/interruption	55 (43.0%)	27 (22.5%)
Related AE	120 (93.8%)	107 (89.2%)
Related AE leading to withdrawal from treatment	7 (5.5%)	14 (11.7%)
Related AE leading to dose modification/interruption	49 (38.3%)	26 (21.7%)

Source: t_ae_oview_SE_26JUN2023_40336

For the purposes of labeling the Applicant is proposing Table 28 below for the USPI to reflect the safety profile observed in ALINA.

Table 28 Applicant - (b) (4)

(b) (4)

[g] Includes bradycardia and sinus bradycardia.

The Applicant's Position: The safety results from the ALINA study demonstrated that alectinib 600 mg BID was generally well tolerated in patients with Stage IB–IIIA ALK-positive NSCLC after surgical resection. The overall safety profile of alectinib was generally consistent with the known risks of alectinib. No significant safety concerns were identified in this study. The USPI will be updated to include the safety results of the ALINA study.

The FDA's Assessment:

FDA sent an information request during labeling negotiations with the Applicant to address differences in rates of AEs reported. On March 28, 2024, the Applicant responded and indicated that some AEs were excluded from the table proposed for the USPI if they were not clearly due to alectinib. (b) (4)

FDA does not agree with excluding these events given the difficulty in accurately assigning attribution of adverse events to study therapy. FDA did not perform an independent analysis of the incidence of drug-related adverse events. The FDA review includes all-causality adverse events and the use of grouped terms.

The summary of treatment emergent adverse events in patients treated in ALINA is provided in Table 29 below.

Table 29 FDA – Summary of Treatment Emergent Adverse Events in Patients Treated in ALINA

	Alectinib N = 128 n (%)	Chemotherapy N = 120 n (%)
All treatment emergent adverse events	126 (98)	112 (93)
Grade 3-4	38 (30)	37 (31)
Fatal treatment emergent adverse events	0	0
Serious adverse events	17 (13)	10 (8)
Adverse events leading to discontinuation	7 (5)	15 (13)
Adverse events leading to dose interruption	35 (27)	22 (18)

Adverse events leading to dose reduction	33 (26)	12 (10)

Source: FDA analyses of the Applicant submitted data ADAE; DCO: June 26, 2023.

Treatment emergent adverse events reported in ≥10% of patients treated with alectinib in ALINA are presented in Table 30 below.

Table 30 FDA – Most Common Treatment Emergent Adverse Events (≥10%) in Patients Treated in ALINA

Adverse Event	ALECENSA N=128		Chemotherapy N = 120	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hepatobiliary System Disorders				
Hepatotoxicity[a]	61	4 *	13	0
Gastrointestinal Disorders				
Constipation	42	0 *	25	0 *
Abdominal pain[b]	13	0	10	1 *
Diarrhea[c]	13	0 *	9	1 *
Musculoskeletal				
Myalgia[d]	34	0 *	1.7	0
Infections and Infestations				
COVID-19	29	0	0.8	0
General Disorders and Administration Site Conditions				
Fatigue[e]	25	0 *	28	4 *
Edema[f]	16	0	1.7	0
Skin and Subcutaneous Tissue Disorders				
Rash[g]	23	1.6	10	0
Respiratory System Disorders				
Cough[h]	20	0 *	3.3	0
Dyspnea[i]	13	0 *	2.5	0
Renal				
Renal Impairment[j]	16	0 *	9	0
Nervous System Disorders				
Dysgeusia[k]	13	0	3.3	0
Headache	11	0	7	0

Investigations				
Increased weight	13	0 *	0.8	0
Cardiac Disorders				
Bradycardia[l]	12	0	0	0

Source: FDA analyses of the Applicant submitted data ADSL and ADAE; DCO: June 26, 2023.
Based on NCI CTCAE v5.0
* All events are Grade 3.
[a] Includes increased alanine aminotransferase, increased aspartate aminotransferase, increased bile acids, increased conjugated bilirubin, increased blood bilirubin, increased unconjugated blood bilirubin, increased gamma-glutamyltransferase, hepatotoxicity, hyperbilirubinemia, increased liver function test, ocular icterus and increased transaminases.
[b] Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, abdominal tenderness, epigastric discomfort and gastrointestinal pain.
[c] Includes colitis and diarrhea.
[d] Includes muscle fatigue, muscular weakness, musculoskeletal chest pain, musculoskeletal stiffness and myalgia.
[e] Includes asthenia and fatigue.
[f] Includes edema, face edema, localized edema, peripheral edema, face swelling and peripheral swelling.
[g] Includes acneiform dermatitis, bullous dermatitis, drug eruption, eczema, rash, erythematous rash, maculo-papular rash, papular rash, seborrheic dermatitis, urticaria and, xeroderma.
[h] Includes cough and productive cough.
[i] Includes dyspnea and exertional dyspnea.
[j] Includes azotemia, increased blood creatinine, decreased renal creatinine clearance, decreased glomerular filtration rate, hypercreatininemia, renal failure and renal impairment.
[k] Includes dysgeusia and taste disorder.
[l] Includes bradycardia and sinus bradycardia.

Laboratory Findings

Data:

Laboratory data: Categorized according to NCI-CTCAE v5.0 and summarized as clinically relevant shifts from baseline per treatment arm (defined as shift from Grade 0, 1, or 2 at baseline to Grade 3 or 4 post-baseline).

Hematology: Clinically meaningful shifts reported in ≥2% of patients were: lymphocytes (low) (3/128 [2.3%]) in the alectinib arm and total absolute neutrophil counts (and total leukocyte count (low)in the chemotherapy arm).

Chemistry: Clinically meaningful shifts reported in ≥2% of the patients were: creatine kinase (high), ALT (high), bilirubin (high) and magnesium (high).

A shift of uric acid post-baseline was reported in 39/113 patients (34.5%) in the alectinib arm and 23/114 patients (20.2%) in the chemotherapy arm. However, these were not considered to be clinically meaningful shifts. Further analysis is ongoing.

No confirmed Hy`s law cases were observed in the ALINA study. Please refer to section 8.2.5.

For the purposes of labeling, the Applicant is proposing Table 31 below for the USPI to reflect the laboratory abnormalities that worsened from baseline occurring in ≥20% of patients treated with alectinib.

Table 31 Applicant - Laboratory Abnormalities that Worsened from Baseline (≥20% of Patients Treated with Alectinib)

Parameter	ALECENSA N= 128		Chemotherapy N=120	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Chemistry				
Increased CPK	77	8	8	1.7
Increased AST	75	0.8	25	0
Increased bilirubin	68	2.3*	4.2	0
Increased alkaline phosphatase	64	0	14	0
Increased ALT	57	2.3	28	0
Increased creatinine	41	0	23	0
Hematology				
Decreased hemoglobin	69	0	67	0.8

Source: t_lb_event_SE_ALINA; t_lb_ctc_shifthigh_SE_26JUN2023_40336; t_lb_shift_creatn_SE_GRPS1.
Based on NCI CTCAE v5.0

The Applicant's Position: In general, differences should be viewed in light of the differences in treatment exposure and lab monitoring period between treatment arms. The evaluation of clinical laboratory parameters showed a higher frequency of increased uric acid in patients treated with alectinib in comparison to chemotherapy. This finding is currently undergoing further assessment. The results of the assessment will be provided in DSR No. 1126783 as part of the dossier. There were no other further findings of clinical relevance.

The FDA's Assessment:
FDA agrees with the Applicant's position regarding shifts in laboratory values, with the exception that increased uric acid worsening from baseline occurred in 30% for all grades and 0% for grade 3 – 4 in the alectinib arm, and 19% for all grade and 0% for grade 3 – 4 in the chemotherapy arm. In addition to the parameters listed in the Applicant's Table 31 above, increased uric acid will be included in the USPI as this was thought to represent a clinically meaningful shift from baseline.

Vital Signs

Data: Body temperature, pulse rate (beats/min), respiratory rate (breaths/min), systolic blood pressure (mmHg), and diastolic blood pressure (mmHg), were collected for the ALINA study.

A higher proportion of patients with a baseline pulse rate of 60-100 beats/min in the alectinib arm experienced abnormally low pulse rate (<60 beats/min) post-baseline compared with the chemotherapy arm (47.2% vs. 0.9%).

The Applicant's Position: The analysis of vital signs did not yield any further findings of clinical relevance or unexpected outcomes.

The FDA's Assessment:
FDA agrees with the Applicant's position regarding the analysis of vital signs. The proportion of patients in the alectinib arm with a normal baseline pulse rate experiencing an abnormally low pulse rate compared with the chemotherapy arm is consistent with the known adverse event of bradycardia, which is listed within the Warnings and Precautions section of the USPI.

Electrocardiograms (ECGs)

Data: A comparable proportion of patients in both treatment arms were reported to have normal ECG findings (88.3% in alectinib arm and 70.0% in chemotherapy arm) or abnormal, not clinically significant ECG findings (53.1% in alectinib arm and 48.3% in chemotherapy arm).

In the alectinib arm, a post-baseline decrease in median heart rate values was observed, with values decreasing from a median of 73 beats/min at baseline, plateauing between Week 3 (median of 66 beats/min) and Week 24 (median of 62 beats/min; heart rate not assessed between these two visits), to 60 beats/min at Week 60.

One patient in each treatment arm (0.8% in the alectinib arm and 0.9% in the chemotherapy arm) experienced post-baseline QTcF prolongation >500 msec. The proportion of patients with a maximum individual change from baseline QTcF of >60 msec was 4.8% in the alectinib arm and 1.8% in the chemotherapy arm. In the categorical ECG analysis for PR and QRS, changes from baseline in PR and QRS duration which met the pre-specified outlier criteria were each observed in 2 patients in the alectinib arm (< 2%). There were no QT prolongation AEs reported in the alectinib arm, while there was one patient with such an event in the chemotherapy arm.

The Applicant's Position: The ECG monitoring differed between treatments arms, with patients in the alectinib arm having more frequent assessments and a longer treatment duration. The ECG analysis confirmed a decrease of heart rate as a known treatment effect of alectinib. No further findings of clinical relevance or unexpected outcomes were observed.

The FDA's Assessment:
FDA agrees with the Applicant's position regarding analysis of ECG findings.

QT

Data: QT results are presented in the section above.

The Applicant's Position: The analysis of ECG QT interval results did not yield any findings of clinical relevance or unexpected outcomes.

The FDA's Assessment:
FDA agrees with the Applicant's position.

Immunogenicity

The Applicant's Position: Not applicable

The FDA's Assessment:
FDA agrees with the Applicant's position.

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant's Position: No per protocol adverse events of special interest were reported in ALINA. This includes no findings of an elevated ALT or AST (post-baseline ALT and AST >3X upper limit of normal [ULN] in combination with either an elevated total bilirubin [>2X ULN] or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia, considered to be an indicator of severe liver injury, as defined by Hy's Law) were reported in ALINA.

The FDA's Assessment:

Hepatotoxicity

FDA evaluated hepatoxicity using a grouped term which included preferred terms of abnormal hepatic function, cholestasis, drug-induced liver injury, hepatotoxicity, hyperbilirubinemia, hypertransaminasemia, increased ALT, AST, blood bilirubin, bile acids, conjugated blood bilirubin, gamma-glutamyltransferase, liver function tests, transaminases, and unconjugated blood bilirubin, jaundice, liver disorder, and ocular icterus. Hepatotoxicity was reported in 61% of alectinib-treated patients in the ALINA trial, including grade ≥3 hepatoxicity in 4.7%.

The rate of any grade hepatotoxicity in patients treated with alectinib in the overall pooled safety dataset was lower at 41% compared to the rate of hepatotoxicity in the ALINA trial, while the incidence of grade ≥ 3 hepatotoxicity was 8%.

Treatment discontinuation due to hepatotoxicity occurred in 1.6% of patients who received alectinib in the ALINA trial and 3.6% of patients in the overall pooled safety dataset.

An information request was sent to the Applicant asking for a potential explanation regarding the higher rates of hepatotoxicity in the adjuvant setting versus the metastatic setting. The Applicant responded to the information request on March 12, 2024, noting that the higher rate of hepatotoxicity in the adjuvant setting was likely due to more frequent safety monitoring (e.g., all laboratory assessments) over a longer duration of time for patients on the alectinib arm of ALINA compared with patients who received alectinib in the metastatic NSCLC setting, with which the FDA agrees.

Interstitial lung disease (ILD)/pneumonitis

ILD/pneumonitis was reported in 3 (2.3%) patients treated with alectinib in the ALINA trial, including 1 (0.8%) patient with grade 3 ILD/pneumonitis. Alectinib was discontinued for all 3 patients.

In the overall pooled safety dataset, ILD/pneumonitis occurred in 1.3% of patients treated with alectinib, with 0.4% of patients experienced grade 33 ILD/pneumonitis. Alectinib was discontinued in 0.9% of patients.

Bradycardia

FDA evaluated bradycardia as a grouped term which included the preferred terms of bradycardia and sinus bradycardia. Bradycardia was reported in 12% of patients treated with alectinib in the ALINA trial, with no cases of grade ≥ 3 bradycardia.

In the overall pooled safety dataset, bradycardia occurred in 11% of patients treated with alectinib, with no cases of grade ≥3 bradycardia.

Severe myalgia and creatinine phosphokinase (CPK) elevation

FDA evaluated myalgia as a grouped term which included the preferred terms of muscle disorder, muscle fatigue, muscle weakness, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness and myalgia. Myalgia was reported in 34% of patients treated with alectinib in the ALINA trial, including 0.8% with grade ≥ 3 myalgia. Dosage modifications (interruptions and reductions) due to myalgia occurred in 4.7% of patients.

Myalgia was observed in 31% of patients treated with alectinib in the overall pooled safety dataset, including grade ≥ 3 myalgia in 0.8%. Dosage modifications were required in 2.1% of patients.

In the ALINA trial, elevated CPK occurred in 77% of 128 patients with CPK laboratory data, including 6% of patients with grade ≥ 3 elevations. In the overall pooled safety dataset, of the 491 patients with CPK laboratory data available, elevated CPK occurred in 56% of patients treated with alectinib, including 6% of patients with grade ≥ 3 elevations. Per the Applicant's response, dated March 12, 2024, to an FDA information request, CPK monitoring was done more frequently and for a longer duration in the ALINA trial compared to the metastatic setting, potentially influencing the higher rates of CPK elevation observed in the ALINA trial compared to the metastatic setting.

Renal impairment

FDA evaluated renal impairment as a grouped term which included the preferred terms of acute kidney injury, azotemia, decreased glomerular filtration rate, decreased renal clearance, hypercreatininemia, increased blood creatinine, renal failure and renal impairment. Renal impairment occurred in 16% of patients treated with alectinib in ALINA, including 0.8% of patients with grade ≥ 3 renal impairment. Dosage modifications for renal impairment occurred in 3.1% of patients.

In the overall pooled safety dataset, renal impairment was observed in 12% of patients treated with alectinib, including grade ≥ 3 in 1.7% of patients. Dosage modifications for renal impairment were required for 2.4% of patients.

Hemolytic anemia

Hemolytic anemia was initially reported for alectinib in the postmarketing setting. Assessments for the determination of hemolytic anemia, which were not collected in the earlier trials of alectinib in the metastatic disease setting, were subsequently collected as part of the ALINA trial. Hemolytic anemia was observed in 3.1% of patients treated with alectinib on the ALINA trial.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety and Tolerability

The Applicant's Position: Not applicable.

The FDA's Assessment:
Clinical outcome assessments were completed using the SF-36V2 physical and mental component scores. This data was considered exploratory and is further detailed in section 8.1.2 under the heading "Efficacy Results – Secondary or exploratory COA (PRO) endpoints".

8.2.7. Safety Analyses by Demographic Subgroups

Data:

Adverse Events by Race (Asian/Non-Asian), Safety-Evaluable Patients

Overall, a comparable proportion of Asian and non-Asian patients in each treatment arm experienced at least one AE (98.6% Asian patients and 98.3% non-Asian patients) in the alectinib arm, and 92.6% Asian patients and 94.2% non-Asian patients in the chemotherapy arm.

In the alectinib arm, a similar proportion of Asian and non-Asian patients experienced Grade 3–5 AEs and SAEs. A numerically higher proportion of non-Asian patients experienced AEs leading to withdrawal from treatment compared with Asian patients, and a higher proportion of Asian patients experienced AEs leading to dose modification or interruption compared with non-Asian patients.

The trends in the chemotherapy arm were similar to the alectinib arm in terms of AEs leading to withdrawal from treatment (i.e., higher proportion of patients in the non-Asian subgroup).

Table 32 Applicant - Overview of Adverse Events by Race (Asian vs. non-Asian), Safety-Evaluable Patients

	Alectinib (N=128)		Chemotherapy (N=120)	
	Asian (N=70)	Non-Asian (N=58)	Asian (N=68)	Non-Asian (N=52)
Total number of patients with at least one AE	69 (98.6%)	57 (98.3%)	63 (92.6%)	49 (94.2%)
Total number of AEs	1111	574	625	353
Total number of patients with at least one				
AE with fatal outcome (Grade 5)	0	0	0	0
Grade 3-5 AE	19 (27.1%)	19 (32.8%)	19 (27.9%)	18 (34.6%)
Serious AE	10 (14.3%)	7 (12.1%)	6 (8.8%)	4 (7.7%)
Serious AE leading to withdrawal from treatment	0	1 (1.7%)	2 (2.9%)	2 (3.8%)
Serious AE leading to dose modification/interruption	4 (5.7%)	3 (5.2%)	3 (4.4%)	1 (1.9%)
Related Serious AE	1 (1.4%)	1 (1.7%)	6 (8.8%)	2 (3.8%)
AE leading to withdrawal from treatment	2 (2.9%)	5 (8.6%)	6 (8.8%)	9 (17.3%)
AE leading to dose modification/interruption	34 (48.6%)	21 (36.2%)	14 (20.6%)	13 (25.0%)
Related AE	69 (98.6%)	51 (87.9%)	59 (86.8%)	48 (92.3%)
Related AE leading to withdrawal from treatment	2 (2.9%)	5 (8.6%)	6 (8.8%)	8 (15.4%)
Related AE leading to dose modification/interruption	30 (42.9%)	19 (32.8%)	14 (20.6%)	12 (23.1%)

Source: t_ae_oview_byasian_SE_ALINA

The AEs by PT with notable differences (≥ 20%) between Asian and non-Asian patients in the alectinib arm were (Asian and non-Asian patients, respectively): AST increased (55.7% and 24.1%), blood bilirubin increased (44.3% and 20.7%), weight increased (22.9% and 1.7%), ALT increased (42.9% and 22.4%).

Adverse Events by Sex, Safety-Evaluable Patients

Overall, a comparable proportion of male and female patients in each treatment arm experienced at least one AE (96.3% male patients and 100% female patients in the alectinib arm, and 90.6% male patients and 96.4% female patients in the chemotherapy arm).

In the alectinib arm, the proportion of patients who experienced Grade 3–5 AEs, SAEs, and AEs leading to withdrawal from treatment was similar between male and female patients. AEs leading to dose modification or interruption occurred more frequently in male patients compared with female patients.

Table 33 Applicant - Overview of Adverse Events by Sex, Safety-Evaluable Patients

	Alectinib (N=128)		Chemotherapy (N=120)	
	Female (N=74)	Male (N=54)	Female (N=56)	Male (N=64)
Total number of patients with at least one AE	74 (100%)	52 (96.3%)	54 (96.4%)	58 (90.6%)
Total number of AEs	1063	622	497	481
Total number of patients with at least one				
AE with fatal outcome (Grade 5)	0	0	0	0
Grade 3-5 AE	23 (31.1%)	15 (27.8%)	13 (23.2%)	24 (37.5%)
Serious AE	10 (13.5%)	7 (13.0%)	4 (7.1%)	6 (9.4%)
Serious AE leading to withdrawal from treatment	1 (1.4%)	0	3 (5.4%)	1 (1.6%)
Serious AE leading to dose modification/interruption	3 (4.1%)	4 (7.4%)	2 (3.6%)	2 (3.1%)
Related Serious AE	2 (2.7%)	0	3 (5.4%)	5 (7.8%)
AE leading to withdrawal from treatment	5 (6.8%)	2 (3.7%)	8 (14.3%)	7 (10.9%)

AE leading to dose modification/interruption	29 (39.2%)	26 (48.1%)	13 (23.2%)	14 (21.9%)
Related AE	72 (97.3%)	48 (88.9%)	52 (92.9%)	55 (85.9%)
Related AE leading to withdrawal from treatment	5 (6.8%)	2 (3.7%)	7 (12.5%)	7 (10.9%)
Related AE leading to dose modification/interruption	27 (36.5%)	22 (40.7%)	13 (23.2%)	13 (20.3%)

Source: t_ae_oview_bysex_SE_ALINA

The AEs by PT with notable differences (≥15%) between male and female patients in the alectinib arm were (male and female patients, respectively) anaemia (9.3% and 33.8% and AST increased (31.5% and 48.6%).

Adverse Events by Age (<65 years vs. ≥ 65 years), Safety-Evaluable Patients

Results should be interpreted with caution due to the small number of patients ≥ 65 years old (n=27).

Overall, a comparable proportion of patients aged < 65 years and ≥ 65 years in each treatment arm experienced at least one AE (98.0% [99 of 101 patients] < 65 years and 100% [27 of 27 patients] ≥ 65 years in the alectinib arm, and 93.1% [81 of 87 patients] < 65 years and 93.9% [31 of 33 patients] ≥ 65 years in the chemotherapy arm).

In the alectinib arm, a higher proportion of patients aged ≥ 65 years experienced Grade 3-5 AEs, SAEs, and AEs leading to withdrawal from treatment compared with patients aged < 65 years.

The trends in the chemotherapy arm were similar to the alectinib arm (i.e., the older subgroup experienced more Grade 3-4 AEs and SAEs.

The proportion of patients who experienced AEs leading to dose modification or interruption was similar for patients aged < 65 years and those aged ≥ 65 years in both treatment arms.

Table 34 Applicant - Overview of Adverse Events by Age (<65 Years vs.≥65 Years), Safety-Evaluable Patients

	Alectinib (N=128)		Chemotherapy (N=120)	
	<65 (N=101)	>=65 (N=27)	<65 (N=87)	>=65 (N=33)
Total number of patients with at least one AE	99 (98.0%)	27 (100%)	81 (93.1%)	31 (93.9%)
Total number of AEs	1336	349	765	213
Total number of patients with at least one AE with fatal outcome (Grade 5)	0	0	0	0
Grade 3-5 AE	28 (27.7%)	10 (37.0%)	25 (28.7%)	12 (36.4%)
Serious AE	12 (11.9%)	5 (18.5%)	6 (6.9%)	4 (12.1%)
Serious AE leading to withdrawal from treatment	0	1 (3.7%)	2 (2.3%)	2 (6.1%)
Serious AE leading to dose modification/interruption	6 (5.9%)	1 (3.7%)	3 (3.4%)	1 (3.0%)
Related Serious AE	1 (1.0%)	1 (3.7%)	5 (5.7%)	3 (9.1%)
AE leading to withdrawal from treatment	2 (2.0%)	5 (18.5%)	10 (11.5%)	5 (15.2%)
AE leading to dose modification/interruption	43 (42.6%)	12 (44.4%)	18 (20.7%)	9 (27.3%)
Related AE	95 (94.1%)	25 (92.6%)	78 (89.7%)	29 (87.9%)
Related AE leading to withdrawal from treatment	2 (2.0%)	5 (18.5%)	10 (11.5%)	4 (12.1%)
Related AE leading to dose modification/interruption	38 (37.6%)	11 (40.7%)	18 (20.7%)	8 (24.2%)

Source: t_ae_oview_byage_SE_ALINA

The AEs by PT with notable differences (≥15%) between patients aged < 65 years and ≥ 65 years in the alectinib arm were (patients < 65 years and patients ≥ 65 years, respectively): blood creatinine increased (10.9% [11 patients] and 29.6%[8 patients]), constipation (38.6% [39 patients]and 55.6%[15 patients]), weight increased (16.8% and 0) and blood alkaline phosphatase increased (21.8% [22 patients] and 37.0%[10 patients]).

Adverse Events by Stage, Safety-Evaluable Patients

Results should be interpreted with caution due to the small number of patients in each subgroup.

The proportion of patients in each treatment arm with Stage IB, Stage II, and Stage IIIA disease who experienced at least one AE was comparable (94.1%[16 of 17 patients], 100%[42 of 42 patients], and 98.6%[68 of 69 patients], respectively, in the alectinib arm and 88.9%[8 of 9 patients], 93.3%[42 of 45 patients], and 93.9%[62 of 66 patients], respectively, in the chemotherapy arm).

In the alectinib arm, the proportion of patients who experienced Grade 3-5 AEs was lower in patients with Stage II NSCLC compared with patients with Stage IB and Stage IIIA NSCLC. The proportion of patients who experienced SAEs was similar across disease stages. The proportion of patients who experienced AEs leading to withdrawal from treatment and AEs leading to dose modification or interruption was higher in patients with Stage IB NSCLC compared with patients with Stage II and Stage IIIA NSCLC.

The AEs by PT with notable differences (≥20%) between patients between any two stages of NSCLC in the alectinib arm were (Stage IB, Stage II, and Stage IIIA, respectively): AST increased (17.6%[3 patients], 47.6%[20 patients], and 43.5%[30 patients]), anaemia (0, 26.2%[11 patients], and 27.5%[19 patients]), blood CPK increased (23.5%[4 patients], 40.5%[17 patients], and 49.3%[34 patients]),COVID-19 (11.8%[2 patients], 26.2%[11 patients], and 34.8%[24 patients]).

Table 35 Applicant - Overview of Adverse Events by Stage (Stage IB, Stage II and Stage IIIA), Safety-Evaluable Patients

	Alectinib (N=128)			Chemotherapy (N=120)		
	Stage IB (N=14)	Stage II (N=46)	Stage IIIA (N=68)	Stage IB (N=11)	Stage II (N=44)	Stage IIIA (N=65)
Total number of patients with at least one AE	13 (92.9%)	46 (100%)	67 (98.5%)	9 (81.8%)	43 (97.7%)	60 (92.3%)
Total number of AEs	143	609	933	56	367	555
Total number of patients with at least one						
AE with fatal outcome (Grade 5)	0	0	0	0	0	0
Grade 3-5 AE	5 (35.7%)	11 (23.9%)	22 (32.4%)	1 (9.1%)	15 (34.1%)	21 (32.3%)
Serious AE	2 (14.3%)	5 (10.9%)	10 (14.7%)	0	5 (11.4%)	5 (7.7%)
Serious AE leading to withdrawal from treatment	0	0	1 (1.5%)	0	2 (4.5%)	2 (3.1%)
Serious AE leading to dose modification/ interruption	2 (14.3%)	1 (2.2%)	4 (5.9%)	0	1 (2.3%)	3 (4.6%)
Related Serious AE	0	0	2 (2.9%)	0	4 (9.1%)	4 (6.2%)
AE leading to withdrawal from treatment	2 (14.3%)	3 (6.5%)	2 (2.9%)	0	5 (11.4%)	10 (15.4%)
AE leading to dose modification/interruption	8 (57.1%)	15 (32.6%)	32 (47.1%)	1 (9.1%)	8 (18.2%)	18 (27.7%)
Related AE	13 (92.9%)	43 (93.5%)	64 (94.1%)	9 (81.8%)	42 (95.5%)	56 (86.2%)
Related AE leading to withdrawal from treatment	2 (14.3%)	3 (6.5%)	2 (2.9%)	0	5 (11.4%)	9 (13.8%)
Related AE leading to dose modification/ interruption	7 (50.0%)	15 (32.6%)	27 (39.7%)	1 (9.1%)	8 (18.2%)	17 (26.2%)

Source t_ae_oview_bystage_SE_ALINA

The Applicant's Position: Some distinctions among the treatment arms within subgroups were noted, however, the overall safety profile did not show any clinically relevant differences in the subgroups.

The FDA's Assessment:
FDA agrees with the Applicant's position that, in general, there were some minor differences in the safety profile between subgroups within treatment arms and that the subgroups were relatively small. However, in the evaluation of the safety profile of alectinib in Asians vs non-Asians, there were relatively large differences (≥ 20%) with AST, ALT, and blood bilirubin elevations reported more frequently in Asian patients, as well as a higher incidence of AEs leading to dose modifications/reductions for Asian patients (49% in Asians vs 36% in non-Asians). It appears the increased incidence of AEs in the Asian subpopulation can largely be managed with dose modifications and interruptions, given the lower rate of treatment discontinuation due to AEs in Asians (2.9%) compared to non-Asians (9%).

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position: No studies were conducted to evaluate a specific safety concern.

The FDA's Assessment:
FDA agrees with the Applicant's position.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position: An exploratory analysis of clinical safety data to support the nonclinical carcinogenicity assessment showed no indication for an association between alectinib and the development of second primary malignancies (SPM) (DSR No: 1119726). The incidence of SPM in patients treated with alectinib in the advanced or metastatic setting (1.0%) was within the range of the background incidence of SPM in the NSCLC population from epidemiological sources (3.5%-15.5%), including studies where Second Primary Lung Cancer (SPLC) was reported as an adverse event in NSCLC patients (1.03%-16.1%). The two SPM events in the ALINA study (new primary NSCLC metastatic and bladder cancer) with the incidence of 1.6% did not alter the conclusion of the DSR No. 1119726 that no indication for an association between alectinib and the development of SPM could be identified.

The FDA's Assessment:
FDA agrees with the Applicant regarding human carcinogenicity or tumor development and that the rate of SPM for patients treated with alectinib was within the background incidence of SPM in the NSCLC population. See Section 5 regarding further carcinogenicity assessment.

Human Reproduction and Pregnancy

The Applicant's Position: At the CCOD, no pregnancies were reported in the study.

The FDA's Assessment:
FDA agrees with the Applicant's position.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position: The Initial Pediatric Study Plan (iPSP) waiver request was submitted to the Agency on 19 March 2018 (IND 111723, Serial No. 0443). The Agreed iPSP – Agreement Letter was issued on 30 August 2018 (Reference ID: 4314373).

The FDA's Assessment:
FDA agrees with the Applicant's position.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position: No new information is provided in the current submission.

The FDA's Assessment:
FDA agrees with the Applicant's position.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position: Since the IBD until PBRER DLP (3 July 2023), an estimated cumulative total of (b) (4) patients have received alectinib from marketing experience (Japan, n= (b) (4); United States, n= (b) (4); European Economic Area [EEA], n= (b) (4); and Rest of World [ROW], n = (b) (4). No new safety concerns were identified. The safety profile of alectinib observed in the post marketing setting is consistent with the safety profile seen in clinical trials.

The FDA's Assessment:
FDA agrees with the Applicant's position that the safety profile of alectinib observed in the postmarketing setting is consistent with the safety profile seen in clinical trials. Hemolytic anemia was identified as an adverse reaction of alectinib in the postmarketing setting and was added to the Warnings and Precautions section of the alectinib USPI prior to the submission of this sNDA. Additional assessments were performed in ALINA for hemolytic anemia, which were not done for trials of alectinib in the metastatic setting, and the data regarding its incidence rate were added to the relevant subsection of the Warnings and Precautions section of the USPI.

Expectations on Safety in the Postmarket Setting

The Applicant's Position: Not applicable

The FDA's Assessment:
FDA agrees with the Applicant's position. There is considerable postmarketing experience with alectinib and no safety updates from the postmarketing setting were included in the USPI with this application.

8.2.11. Integrated Assessment of Safety

Data: Pooled safety data from the mNSCLC population are summarized side by side and pooled with ALINA data to support contextualizing the safety profile observed in the ALINA study. Data should be reviewed considering the differences in disease populations, reporting variability (studies separated in time and study conduct), and lines of therapy. Additionally, the duration/frequency of safety monitoring (e.g., all laboratory assessments) and treatment duration was longer in the ALINA study.

Exposure: The median treatment duration was 23.9 months (range: 0-25) in ALINA and 14.8 months (range: 0-63) in the mNSCLC Population.

Table 36 Applicant – Overview of AEs

	Alectinib 600mg BID: BO40336 (N=128)	Alectinib 600mg BID: NP28761, NP28673, BO28984 (N=405)	Alectinib 600mg BID: NP28761, NP28673, BO28984, BO40336 (N=533)
Total number of patients with at least one AE	126 (98.4%)	397 (98.0%)	523 (98.1%)
Total number of AEs	1685	5250	6935
Total number of patients with at least one			
AE with fatal outcome (Grade 5)	0	14 (3.5%)	14 (2.6%)
Grade 3-5 AE	38 (29.7%)	189 (46.7%)	227 (42.6%)
Serious AE	17 (13.3%)	129 (31.9%)	146 (27.4%)
Serious AE leading to withdrawal from treatment	1 (0.8%)	22 (5.4%)	23 (4.3%)
Serious AE leading to dose modification/interruption	7 (5.5%)	61 (15.1%)	68 (12.8%)
Related Serious AE	2 (1.6%)	30 (7.4%)	32 (6.0%)
AE leading to withdrawal from treatment	7 (5.5%)	37 (9.1%)	44 (8.3%)
AE leading to dose modification/ interruption	55 (43.0%)	145 (35.8%)	200 (37.5%)
Related AE	120 (93.8%)	320 (79.0%)	440 (82.6%)
Related AE leading to withdrawal from treatment	7 (5.5%)	24 (5.9%)	31 (5.8%)
Related AE leading to dose modification/interruption	49 (38.3%)	93 (23.0%)	142 (26.6%)

Source: t_ae_oview_SE_GRPS1

Key results in the ALINA (adjuvant) and mNSCLC (metastatic) populations are summarized below (expressed as ALINA and mNSCLC, where applicable):

Grade 5 AEs: No Grade 5 AEs were reported in ALINA.

Serious and Severe events: Consistent with the disease population, more patients experienced serious or severe (Grade 3-5) adverse events in mNSCLC population than the ALINA population. The most frequently (> 1.0% of patients in either population) reported SAEs by PT was pneumonia (2.3% and 4.0%). The most frequently reported Grade 3-5 AE by PT was blood CPK increased (6.3%) in ALINA and anemia (4.2%) in the mNSCLC population.

Common AEs : The most frequently (³ 20% of patients in either population) reported AEs by PT were constipation (42.2% and 37.5%), fatigue (14.1% and 29.6%), myalgia (28.1% and 22.7%) AST increased (41.4% and 16.8%), oedema peripheral (10.2% and 25.4%), anaemia (23.4% and

20.7%), blood bilirubin increased (33.6% and 16.3%), ALT increased (33.6% and 15.8%), blood CPK increased (43.0% and 11.6%).

Dose discontinuation or modification (ALINA and mNSCLC): The proportion of patients who experienced AEs leading to treatment discontinuation (5.5% and 9.1%) and dose interruption (27.3% and 30.4%) were similar in the ALINA and mNSCLC populations. More patients experienced AEs leading to dose reductions in the ALINA population (25.8% and 16%).

Selected AEs: The data was largely comparable across ALINA and mNSCLC populations with a few notable exceptions:

- The proportion of patients with Grade 3-5 selected AEs, and selected SAEs, were lower in the ALINA population compared to mNSCLC population.
- A higher proportion of patients reported at least one AE of hepatocellular or cholestatic damage, or abnormal liver function tests in ALINA population (60.9%) compared to mNSCLC population (36.0%). This difference is mainly driven by a higher frequency in AST, ALT and blood bilirubin increases in the ALINA setting compared to mNSCLC population (41.4% and 16.8%, 33.6% and 15.8% and 33.6% and 16.3%, respectively). Notably, the proportion of patients experiencing Grade 3-5 AEs was lower in the ALINA population and the mNSCLC (4.7% and 9.6%). No patients in ALINA experienced SAEs compared to 2.5% in the mNSCLC population. The proportion of patients who experienced AEs leading to treatment discontinuations was lower in the ALINA population (1.6% and 4.4%) and both groups had similar rates of dose reduction or interruptions (14.1% and 11.6%). The median time to onset of AST and ALT increases was similar in both groups (ALINA 28.5 days and mNSCLC 29 days). The median time to elevation of bilirubin was 43 days in the ALINA population and 64 days in the mNSCLC population.
- A higher proportion of patients reported at least one muscular or CPK elevation AE in ALINA population (71.9%) compared to mNSCLC population (53.8%). This difference is mainly driven by a higher frequency in CPK elevations (43.0% and 11.6%). However, the proportion of patients who experienced myalgia was similar in both groups (28.1% in ALINA and 22.7% in mNSCLC). The proportion of patients who experienced Grade 3-5 CPK increases was comparable between treatment groups (6.3% in ALINA and 3.7% in mNSCLC). No patient experienced serious CPK increases in the ALINA population and 0.2% had a serious CPK increase in the mNSCLC population. No treatment discontinuations were reported in either group and dose reductions or interruptions were reported with a higher frequency in the ALINA population (10.9% and 3.5%). The median time to CPK elevation was the same in both groups (15 days).

The Applicant's Position: The safety results of alectinib observed in ALINA were generally consistent with the safety profile established in the mNSCLC clinical studies. While there were differences in frequencies observed for some known risks, [caveated by cross-study differences, study population], most of the events were low grade and non-serious and did not impact the

patient's ability to receive treatment with alectinib. The current management guidance included in the labels for these identified risks remains adequate.

The FDA's Assessment:

In general, FDA agrees with the Applicant's position. The types of adverse events reported in patients treated with alectinib in the ALINA trial were consistent with those previously observed in those treated with alectinib in the metastatic setting. While the incidence rates of common adverse reactions were generally similar to those observed between ALINA and the metastatic pooled safety dataset, serious adverse events and grade 3-5 adverse events were more common in the metastatic pooled safety dataset compared to ALINA. Rates of adverse events leading to drug discontinuation and dose interruption were similar in ALINA and the metastatic pooled safety dataset, while rates of adverse events leading to dose reductions were higher in ALINA compared to the metastatic pooled safety dataset.

Key adverse events of interest were hepatotoxicity, interstitial lung disease/pneumonitis, renal impairment, bradycardia, myalgia and creatinine phosphokinase (CPK) elevation, and hemolytic anemia. While the incidence rates of hepatotoxicity and CPK elevations were higher in ALINA compared to those in the metastatic studies, incidence rates of ILD/pneumonitis, renal impairment, bradycardia, and myalgia were similar between ALINA and the metastatic studies. These safety concerns are adequately addressed by information in the Warnings and Precautions section and the dose modification recommendations included in product labeling.

Analysis of the HRQoL data from the SF-36V2 questionnaire was considered exploratory. In addition, claims of detrimental impact (or lack thereof) from adjuvant therapy are a tolerability consideration and were not sufficiently measured using SF-36v2 alone.

In summary, the overall safety profile of alectinib is similar to that previously reported and is acceptable for use in the adjuvant setting, in the context of treatment of a life-threatening disease in a curative intent setting.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

The statistical assessment of efficacy was based on the submitted data and results of the ALINA trial in which the primary endpoint, investigator-assessed DFS, compared alectinib to platinum-based chemotherapy as adjuvant treatment following tumor resection for patients with ALK-positive NSCLC. Investigator-assessed DFS was hierarchically tested in patients with Stage II-IIIA NSCLC and then, if statistically significant, in the ITT population. One interim analysis of investigator-assessed DFS was planned at a 66% information fraction for patients with stage II-IIIA NSCLC. Lan-DeMets approximation of O'Brien-Fleming boundary values were used to control overall study-wise Type I error rate at a one-sided alpha of 0.025. The efficacy results submitted in this marketing application are from this prespecified interim analysis.

No major statistical issues were identified; however, FDA has the following comments:

1. Major protocol deviations due to missed disease assessments in ALINA were relatively high (occurring for 14.6% of patients in the alectinib arm and 18.1% of patients in the chemotherapy arm). Reasons for missing disease assessments by treatment arm is provided in the *Protocol violations/deviations* section above. Additionally, according to the Applicant, there was only one patient in the chemotherapy arm who had two consecutive disease assessments prior to a DFS event. FDA review and assessments of these protocol deviations indicate that it is unlikely that the impact of the missing disease assessments will change the interpretation of the primary efficacy outcome results of investigator-assessed DFS.

2. The ALINA statistical analysis plan (SAP) version 2.0 included a sensitivity analysis plan for DFS censoring patients from sites in Russia and/or Ukraine due to a potential inability to conduct site inspections or source data verification. A sensitivity analysis censoring patients from these enrollment sites was performed on February 24, 2022. These results appear to be consistent with the primary analysis of DFS.

3. The censoring rule of the primary endpoint, DFS as assessed by investigator, is different from FDA's general recommendation to censor patients who receive a new anti-cancer therapy at the time of receipt of the new anti-cancer therapy. However, only 5 patients received new anti-cancer therapies. Due to the small number of patients who received new anti-cancer therapy, the impact of not censoring these patients for new anti-cancer therapy likely has minimal impact on the interpretation of the results of DFS as assessed by investigator.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The ALINA trial is a global, multicenter, open-label, randomized, controlled trial of 257 patients with stage IB (tumors ≥ 4 cm) to stage IIIA (per the 7th edition of TNM staging by the AJCC) ALK-positive NSCLC after complete tumor resection, who were randomized (1:1) to receive either 24 months of alectinib or 4 cycles of protocol-specified platinum-based chemotherapy. At the time of the pre-planned interim analysis, treatment with alectinib demonstrated a statistically significant and clinically meaningful improvement in the primary efficacy outcome of DFS over chemotherapy in the population of patients with stage II-IIIA and stage IB-IIIA (overall population) NSCLC. The safety profile of alectinib is acceptable for the intended population and is sufficiently informed by product labeling.

Therefore, given the robust effect of alectinib on DFS observed in the ALINA trial in both the stage II-IIIA and overall populations, and the use of DFS to support traditional approvals of adjuvant therapy in NSCLC and other tumor types, FDA considers the current analysis to provide substantial evidence of effectiveness of alectinib in the adjuvant setting.

Based on a favorable risk-benefit assessment of alectinib, the FDA review teams recommend traditional approval for the following indication:

ALECENSA (alectinib) is indicated as adjuvant treatment in adult patients following tumor resection of anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) (tumors ≥4 cm or node positive), as detected by an FDA-approved test.

X	X
Arup Sinha, PhD Primary Statistical Reviewer	Xiaoxue Li, PhD Statistical Team Leader
X	X
Primary Clinical Reviewer	Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

FDA did not refer this supplemental application to an advisory committee as no significant efficacy or safety issues were identified during the review that required external input for the proposed indication.

10 proposed indication. Pediatrics

The Applicant's Position: Not Applicable as the applicant has not proposed any pediatric sections in the proposed labeling.

The FDA's Assessment:

FDA agrees with the Applicant's statement above.

11 Labeling Recommendations

Data:

Table 37 Applicant - Summary of Significant Labeling Changes

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's Proposed Labeling**
1.1 Indications and Usage, Adjuvant Treatment of ALK+ NSCLC	(b) (4)	Revised the indication statement to accurately reflect the patients enrolled in the trial, e.g., adult patients following tumor resection of ALK-positive NSCLC (tumors ≥ 4 cm or node positive).
2.1 Dosage and Administration, Patient Selection	Updated to capture resected ALK+ NSCLC patients.	FDA agrees with proposal.
2.2 Dosing and Administration, Duration of Treatment	Included recommended dosing regimen for resected ALK+ NSCLC.	Reformatted proposed text to table format to improve clarity.
5 Warnings and Precautions	(b) (4)	Section 5 (b) (4) We revised this to "pooled safety population" with a cross reference to Section 6.1 of the USPI to describe these patients.
6.1 Adverse Reactions, Clinical Trial Experience, Adjuvant Treatment of	Included information from ALINA.	FDA inserted a description of the pooled safety population (N=533).

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

ALK+ NSCLC		FDA adjudicated all safety data for the ALINA study.
6.2 Postmarketing Experience	Section deleted as hemolytic anemia has now been observed in clinical trial setting and is elaborated on in Section 5.6. WARNINGS AND PRECAUTIONS – Hemolytic Anemia of the USPI.	FDA agrees with the deletion. Prior to the submission of this sNDA, hemolytic anemia was listed in Section 5.6. This section was updated with data from the ALINA trial.
8.5 Geriatric Use	Updated to include information across registrational studies	FDA agrees with the update of N=533. Editorial revisions.
14.1 Clinical Studies, Adjuvant Treatment of ALK+ NSCLC	Included information from ALINA.	FDA adjudicated all efficacy data for the ALINA study. Editorial revisions.
Patient Information	Updated to reflect use in the adjuvant setting.	Editorial revisions.

The Applicant's Position:

The Applicant believes the efficacy and safety data from ALINA provide substantial evidence to demonstrate a favorable benefit-risk profile for the use of alectinib as adjuvant treatment in ALK-positive NSCLC patients after surgical resection.

The FDA's Assessment:
The format, language, and content of the proposed labeling was evaluated and revised for consistency with 21 Code of Federal Regulations (CFR), labeling guidances and current labeling practices of the Office of Oncologic Diseases. The table summarizes key labeling changes.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The clinical review team determined that a risk evaluation and mitigation strategy (REMS) was not required to ensure the safe and effective use of alectinib for the indicated population given the well-established safety profile and the experience of the medical oncology community in managing adverse reactions associated with alectinib. Recommendations for the safe and effective use of alectinib are provided in the U.S. Prescribing Information as well as in thePatient Information.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:
The following postmarketing requirements (PMRs) and postmarketing commitments (PMCs) will be issued for this application:

1. PMR 4630-1

Conduct a carcinogenicity study in mice to evaluate the potential serious risk for carcinogenicity. Submit a carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

Draft Protocol Submission:	02/2025
Final Protocol Submission:	06/2025
Study Completion:	10/2026
Final Report Submission:	04/2027

Rationale: Because of the anticipated prolonged survival in an adjuvant setting, the risk of carcinogenicity must be characterized. A study in mice is warranted to further characterize the carcinogenic potential of alectinib.

2. PMR 4630-2

Conduct a carcinogenicity study in rats to evaluate the potential serious risk of carcinogenicity. Submit a carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

Draft Protocol Submission:	02/2025
Final Protocol Submission:	06/2025
Study Completion:	07/2028
Final Report Submission:	12/2028

Rationale: Because of the anticipated prolonged survival in an adjuvant setting, the risk of carcinogenicity must be characterized. A study in rats is warranted to further characterize the carcinogenic potential of alectinib.

3. PMR 4630-3

Conduct a GLP fertility study in female rats to evaluate the potential risk of impairment of fertility.

Draft Protocol Submission:	04/2025
Final Protocol Submission:	08/2025
Study Completion:	05/2026
Final Report Submission:	09/2026

Rationale: Because of the anticipated prolonged survival in an adjuvant setting, effects

of alectinib on female fertility must be characterized. A study in female rats is warranted to determine the risk of impairment of fertility from alectinib.

4. PMR 4630-4

Conduct a GLP fertility study in male rats to evaluate the potential risk of impairment of fertility.

Draft Protocol Submission: 04/2025
Final Protocol Submission: 08/2025
Study Completion: 05/2026
Final Report Submission: 09/2026

5. PMC 4630-5

Complete clinical trial ALINA, titled, "A Phase III, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of Adjuvant Alectinib Versus Adjuvant Platinum-Based Chemotherapy in Patients with Completely Resected Stage IB (Tumors ≥ 4 cm) to Stage IIIA Anaplastic Lymphoma Kinase-Positive Non-Small Cell Lung Cancer", to provide the final updated descriptive disease-free survival analyses based on the prespecified final number of events or when all patients have been followed for 5 years, and overall survival analyses when all patients have been followed for 5 years.

Trial Completion: 12/2026
Final Report Submission: 09/2027

Rationale: The primary endpoint of the ALINA trial is to assess the efficacy of alectinib versus chemotherapy in adult patients with resected anaplastic lymphoma kinase (ALK)-positive, stage IB (tumors ≥4 cm) to stage IIIA (based on AJCC 7th edition) non-small cell lung cancer (NSCLC), as measured by disease-free survival (DFS). The median DFS is not reached in the alectinib arm. Overall survival (OS), which is a secondary endpoint that is not being formally tested as part of the statistical analysis plan, is immature at this time. Although DFS is considered an acceptable endpoint to support approval of a therapy in the adjuvant setting, it is important to assess whether the observed improvement in DFS will also translate into an improvement in OS.

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:	Is a PMC/PMR needed?

X	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	_ _ Yes _X_ No There was only one patient who was Black or African American and one patient who was Hispanic or Latino treated with alectinib in ALINA. Although the true incidence of ALK positive NSCLC across racial and ethnic subgroups in the U.S. is not well characterized (perhaps in part related to inconsistent tumor genomic testing), Black or African American and Hispanic or Latino patients were likely underrepresented in ALINA. However, given the pathophysiology of ALK positive NSCLC and alectinib's mechanism of action as a TKI targeting an oncogenic driver mutation, it is expected that the treatment effect of alectinib is consistent across racial and ethnic subgroups. Race and ethnicity are not expected to have clinically meaningful effects on the PK of alectinib. Therefore, a PMC for further evaluation of alectinib in subgroups of patients based on race and ethnicity will not be requested.
X	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g., race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	_ _ Yes _X_ No
X	Other considerations (e.g.: PK/PD), if applicable:	_ _ Yes _X_ No

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

X

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

19 Appendices

19.1. References

The Applicant's References: *Copies of references are available upon request.*

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The FDA's References:

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19.2. Financial Disclosure

The Applicant's Position: For the financial disclosure information for the ALINA study, please see Module 1.3.4.

Covered Clinical Study (Name and/or Number):* ALINA (BO40336)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1035		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
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)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant and confirmed/edited by the FDA.

The FDA's Assessment:
FDA agrees with the Applicant's position.

19.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position: Refer to Section 5.

The FDA's Assessment: None. Refer to Section 5.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Population PK Analysis

19.4.1.1. Executive Summary

The FDA's Assessment:

The PK data of alectinib and its metabolite M4 from study ALINA can be adequately described by the previously assessed popPK model. The findings and conclusions on effect of intrinsic factors are consistent with previous review.

19.4.1.2. PPK Assessment Summary

The Applicant's Position: [Highlight the key findings in the white cells.]

General Information		
Objectives of PPK Analysis		• Evaluate the previously developed population PK models for alectinib and M4 on pharmacokinetic data collected in study ALINA in patients with completely resected stage IB-IIIA ALK-positive NSCLC using external validation approach. • Confirm the effects of covariates which contribute significantly to the between-subject variability in PK parameters of alectinib and M4 in in patients with completely resected stage IB-IIIA ALK-positive NSCLC. • Determine individual estimates for derived secondary PK parameters for exposure-efficacy and exposure-safety analyses and for summary statistics.
Study Included		ALINA (BO40336)
Dose(s) Included		600 mg BID alectinib
Population Included		Patients with completely resected Stage 1B-IIIA ALK-positive NSCLC
Population Characteristics (PopPK Report RDR 1127637)	General	Age median 54 (range 26-80) Weight median 65.6 (range 40.5-120) 52 (41.9%) male, 72 (58.1%) female 53 (42.7%) White, 1 (0.8%) Black, 68 (54.8%) Asian and 2 (1.6%) Unknown .
	Organ Impairment	Hepatic (Child-Pugh, NCI, etc): 106 (85.5%) Normal, 15 (12.1%) Mild and 3 (2.4%) Moderate Renal (CrCL, etc): 69 (55.6%) Normal, 53 (42.7%) Mild and 2 (1.6%) Moderate.
	Pediatrics (if any)	NA
No. of Patients, PK Samples, and BLQ		Total no of patients within alectinib arm = 128 PK-evaluable subjects = 124 Alectinib: Total observations =1170; 126 (9.52%) pre-treatment BLQ/ 20 (1.51%) post-first dose BLQ M4: Total observations =1173; 125 (9.44%) pre-treatment BLQ/ 13 (0.98%) post-first dose BLQ.
Sampling Schedule	Intensive Sampling	Week 3 collections at Pre-dose (within 2 hours before the first administration of alectinib), 0.5, 1, 2, 4, 6, 8, 10, and 12 (optional) hours for first 6 Japanese subjects enrolled.
	In ITT Population	Pre-dose (within 2 hours before the first administration of alectinib) at baseline, and Weeks 3, 6, 9, 12, 24, 36, 48, 60, 72, 84, and 96.
Covariates Evaluated	Static	Age, Weight, Sex, Race, Ethnicity, Smoking History, Cancer Stage, ECOG, Hepatic Impairment, Renal Impairment, serum creatinine, creatinine clearance, alanine aminotransferase, aspartate aminotransferase, total bilirubin
	Time-varying	None
Final Model	**Summary**	**Acceptability [FDA's comments]**

Software and Version	Population PK analyses were performed in the validated PMX environment version 1.1, incorporating in an integrated manner NONMEM version 7.4.4, Pirana version 2.9.9, and PsN version 5.0.0.	Acceptable
Model Structure	Two separate PK models were developed for alectinib and M4. Both alectinib and M4 were best described by a 1-compartment model with first order elimination, with absorption described by a sequential zero-order and first-order process	Acceptable
Model Parameter Estimates (Table 15 and Table 20 from the original popPK report - original NDA 208434)	Alectinib: Typical values of CL/F=1965 L/d, V/F=4016 L, KA=31.2 per day, D1 (Duration of zero-order absorption) =0.143 day M4: Typical values of CL/F=5205 L/d, V/F=10093 L, Kformation=14.2 per day, D1 (Duration of zero-order formation) =0.209 day	Acceptable
Uncertainty and Variability (Table 15 and Table 20 from the original popPK report report - original NDA 208434)	Alectinib: RSE (CL/F) =3.5%, RSE(V/F) =4.3% L, RSE (KA)=18.1%, RSE (D1)=8.5% Eta shrinkage was modest for CL/F and V/F (1.58% and 16.1%, respectively) but higher for KA and D1 (69.9% and 42.2%, respectively M4: RSE (CL/F) =3.1%, RSE(V/F) =6.2% L, RSE (Kformation)=13.6%, RSE (D1)=4.8% Eta shrinkage was modest for CL/F and V/F (1.30% and 12.1%, respectively) but high for Kformation (43.5%)	Acceptable
BLQ for Parameter Accuracy	<1% of post-dose PK concentrations were BLQ and were excluded from the model estimation.	Acceptable
GOF, VPC (popPK report- current sNDA submission)	PopPK report RDR 1127637	Acceptable
Significant Covariates and Clinical Relevance	Body weight is the only significant covariate affecting PK of Alectinib and M4. No other intrinsic or extrinsic factors identified to significantly have impact.	Acceptable
Analysis Based on Simulation (optional)	Table 4 showed popPK-simulated exposure of alectinib and M4 (AUC0-12hr) at steady state by demographic, renal and hepatic function.	Acceptable
Labeling Language	**Description**	**Acceptability**

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

		[FDA's comments]
12.3 PK	No new PK information available that requires a label update	Acceptable

19.4.2. Exposure-Response Analysis

19.4.2.1. ER (efficacy) Executive Summary

The FDA's Assessment:

There is no apparent exposure-efficacy relationship observed between DFS and total alectinib and M4 exposure at 600 mg BID. However, interpretation of this ER relationship is limited as it only contains data from one dose level.

19.4.2.2. ER (efficacy) Assessment Summary

The Applicant's Position: [Highlight the key findings in the white cells.]

General Information			
Goal of ER analysis		Evaluate the relationship between total exposure (alectinib+M4) and disease free survival (DFS) in patients with completely resected Stage IB-IIIA ALK-positive NSCLC	
Study Included		ALINA only	
Endpoint		Primary endpoint: Disease-free survival (DFS) by investigator assessment in patients with stage IB-IIIA Secondary endpoint: Overall Survival (Not evaluated since data is immature)	
No. of Patients (total, and with individual PK)		Total no of patients within alectinib arm = 128 PK-evaluable subjects = 124	
Population Characteristics (ER report: RDR: 1127760)	General	Age median (range): 54 (26-80) Weight median (range): 65.6 (40.5- 120) 52 (41.9%) male, 72 (58.1%) female 53 (42.7%) White, 1 (0.8%) Black, 68 (54.8%) Asian, 2 (1.6%) Unknown	
	Pediatrics (if any)	NA	
Dose(s) Included		600 mg BID	
Exposure Metrics Explored (range)		$C_{avg,ss,total}$: total average plasma concentration of alectinib and M4 at steady state	
Covariates Evaluated		Sex, Race, Ethnicity, Smoking History, Cancer Stage, ECOG, Hepatic Impairment, Renal Impairment	
Final Model Parameters		**Summary**	**Acceptability [FDA's comments]**
Model Structure		Time-to-event endpoints (DFS) were first explored using Kaplan-Meier estimation stratified by quartiles of exposure metrics, then by using Cox regression with exposure metrics as continuous variables.	Acceptable

Model Parameter Estimates	Table 5 of the ER report	Acceptable
Model Evaluation	Model diagnostic was conducted, and the result was shown in Section 19.3.2 in the ER report.	Acceptable
Covariates and Clinical Relevance	As no covariates were identified as related to DFS during the graphical analysis, no covariates were evaluated in the Cox proportional-hazards model.	Acceptable
Simulation for Specific Population	None performed.	Acceptable
Visualization of E-R relationships	Figure 1	Acceptable
Overall Clinical Relevance for ER	Alectinib at 600mg BID showed significant clinical result (DFS). There is no exposure-efficacy relationship observed between DFS and total alectinib and M4 exposure at 600mg BID. No covariates identified as related to DFS.	Acceptable
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	None	Acceptable

19.4.2.3. ER (safety) Executive Summary

The FDA's Assessment:

There was no significant exposure-safety relationship for the occurrences of first serious adverse events (SAEs) or AEs Grade 3 or above following a dosage of 600 mg BID. However, interpretation of this ER relationship is limited as it only contains data from one dose level.

19.4.2.4. ER (safety) Assessment Summary

The Applicant's Position:[Highlight the key findings in the white cells.]

General Information		
Goal of ER analysis		Evaluate the relationship between total exposure (alectinib+M4) and key safety events in patients with completely resected Stage IB-IIIA ALK-positive NSCLC
Study Included		ALINA only
Population Included		Patients with completely resected Stage 1B-IIIA ALK-positive NSCLC
Endpoint		• The occurrences of serious adverse events (SAE) • The occurrences of Adverse events Grade 3 or above (Grade 3+)
No. of Patients (total, and with individual PK)		Total no of patients within alectinib arm = 128 PK-evaluable subjects = 124
Population Characteristics (ER report: RDR: 1127760)	General	• Age median (range): 54 (26-80) • Weight median (range): 65.6 (40.5- 120) • 52 (41.9%) male, 72 (58.1%) female • 53 (42.7%) White, 1 (0.8%) Black, 68 (54.8%) Asian and 2 (1.6%) Unknown

	Organ impairment	• Hepatic (Child-Pugh, NCI, etc): 106 (85.5%) Normal, 15 (12.1%) Mild and 3 (2.4%) Moderate • Renal (CrCL, etc): 69 (55.6%) Normal, 53 (42.7%) Mild and 2 (1.6%) Moderate	
	Pediatrics (if any)	NA	
	Geriatrics (if any)	NA	
Dose(s) Included		600 mg BID alectinib	
Exposure Metrics Explored (range)		$C_{avg,ss,total}$: total average plasma concentration of alectinib and M4 at steady state	
Covariates Evaluated		Sex, Race, Ethnicity, Smoking History, Cancer Stage, ECOG score, Hepatic Impairment, Renal Impairment	
Final Model Parameters		**Summary**	**Acceptability [FDA's comments]**
Model Structure		Safety (binary) endpoints (SAE, Grade 3+ AE) were modeled using logistic regression versus exposure as a continuous variable.	Acceptable
Model Parameter Estimates		ER report RDR: 1127760.	Acceptable
Model Evaluation		Not conducted	Acceptable
Covariates and Clinical Relevance		None of the covariates was statistically significant	Acceptable
Simulation for Specific Population		None performed	Acceptable
Visualization of E-R relationships		ER report RDR: 1127760.	Acceptable
Overall Clinical Relevance for ER		- SAE: No statistically significant relationship between the probability of SAE and total alectinib and M4 exposure - Grade 3+ AE: No statistically significant relationship between the probability of Grade 3+ AE and total alectinib and M4 exposure.	Acceptable
Labeling Language		**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics		None	Acceptable

19.4.2.5. Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position: The magnitude of benefit in this study was strong given the stratified HR of 0.24 (95% CI: 0.13, 0.43; p value < 0.0001), which corresponds to a 76% relative risk reduction of disease recurrence or death with alectinib compared to chemotherapy. The safety results of alectinib observed in ALINA were generally consistent with the safety profile established in the mNSCLC clinical studies. No significant safety concern was identified in the ALINA study. The flat exposure-response relationships between alectinib exposure and efficacy/ safety further supports a positive benefit-risk profile for alectinib at 600mg BID in the proposed indication.

The FDA's Assessment:

FDA agrees that a dosage of 600 mg BID demonstrates a favorable risk-benefit profile in the intended population based on clinical data. Interpretation of exposure-response relationships are limited as analyses only include one dose level.

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

None.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Sachia Khasar, PhD	CDER/OOD/DHOT	Sections: 5	Select one: ___X Authored _X__ Approved
	Signature: Gabriel S. Khasar -S Digitally signed by Gabriel S. Khasar -S Date: 2024.04.17 16:43:17 -04'00'			
Nonclinical Supervisor	Claudia P. Miller, PhD	CDER/OOD/DHOT	Sections: 5	Select one: X__ Authored __X__ Approved
	Signature: Claudia Miller -S Digitally signed by Claudia Miller -S Date: 2024.04.17 16:53:58 -04'00'			
Clinical Pharmacology Reviewer	Justin Collazo, PharmD	CDER/OTS/OCP/DCPII	Sections: 6	Select one: _X__ Authored _____Approved
	Signature: Justin S. Collazo -S Digitally signed by Justin S. Collazo -S Date: 2024.04.17 16:12:05 -04'00'			
Clinical Pharmacology Team Leader	Stacy Shord,Pharm.D.,	CDER/OTS/OCP/DCPII	Sections:	Select one: ___Authored x___Approved
	Signature: See Deputy Director signature			
Clinical Pharmacology Deputy Director	Stacy Shord, Pharm.D.,	CDER/OTS/OCP/DCPII	Sections: 6, 19.4	Select one: ___Authored x___Approved
	Signature: Stacy Shord -S Digitally signed by Stacy Shord -S Date: 2024.04.18 08:08:32 -04'00'			
Clinical Reviewer	Jeevan Puthiamadathil, MD	CDER/OOD/DO2	Sections: 1, 2, 3, 4, 5, 7, 8, 9, 10, 13, 19	Select one: _X_ Authored ___Approved
	Signature: Jeevan M. Puthiamadathil -S Digitally signed by Jeevan M. Puthiamadathil -S Date: 2024.04.17 17:09:43 -04'00'			
Clinical Team Leader	Paz Vellanki, MD Ph.D	CDER/OOD/DO2	Sections: see CTDL	Select one: ___Authored _____Approved

	Signature: see CDTL signature

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical Reviewer	Arup Sinha, PhD	CDER/OTS/DBV	Sections: 8	**Select one:** _X_ Authored ___ Approved
	Signature: see Statistical Team Leader signature			
Statistical Team Leader	Xiaoxue Li, PhD	CDER/OTS/DBV	Sections: 1, 8	**Select one:** _X_ Authored _X_ Approved
	Signature: Xiaoxue Li -S Digitally signed by Xiaoxue Li -S Date: 2024.04.17 16:24:55 -04'00'			
Statistical Deputy Director	Pallavi Mishra-Kalyani, PhD	CDER/OTS/DBV	Sections: 1, 8	**Select one:** ___ Authored _X_ Approved
	Signature: Pallavi S. Mishra-kalyani -S Digitally signed by Pallavi S. Mishra-kalyani -S Date: 2024.04.18 09:03:50 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Paz Vellanki, MD PhD	CDER/OOD/DO2	Sections: All	**Select one:** _X_ Authored _X_ Approved
	Signature: Refer to electronic signature in DARRTS			
Associate Director for Labeling (ADL)	Barbara Scepura, MSN, CRNP	CDER/OOD	Section: 11	**Select one:** _x_ Authored ___ Approved
	Signature: Barbara A. Scepura -S Digitally signed by Barbara A. Scepura -S Date: 2024.04.17 17:02:35 -04'00'			
Supervisory Associate Director (Clinical)	Erin Larkins, MD	CDER/OOD/DO2	Sections: All	**Select one:** ___ Authored _X_ Approved
	Signature: Refer to electronic signature in DARRTS			

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PAZ J VELLANKI
04/18/2024 02:00:41 PM

ERIN A LARKINS
04/18/2024 02:08:44 PM