25 April 2024
EMA/240552/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Alecensa

International non-proprietary name: Alectinib

Procedure No. EMEA/H/C/004164/II/0047

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Description
ADR	adverse drug reactions
AE	adverse event
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
aNSCLC	advanced non-small cell lung cancer
AST	aspartate aminotransferase
BID	twice a day
BLQ	below the lower limit of quantification
CALGB	Cancer and Leukemia Group B
CCOD	clinical cutoff date
CE	Conformité Européenne
CL/F	apparent plasma clearance
CNS	central nervous system
CPK	creatine phosphokinase
CSR	clinical study report
DFS	disease-free survival
ECOG	Eastern Cooperative Oncology Group
E-R	Exposure-response
ESMO	European Society for Medical Oncology
E.U.	European Union
HR	hazard ratio
iDMC	independent Data Monitoring Committee
INV	Investigator
IRC	Independent Review Committee
ITT	intent-to-treat
KM	Kaplan-Meier
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
mNSCLC	metastatic non–small cell lung cancer

NSCLC	non–small cell lung cancer
NE	not estimable
OS	overall survival
PK	pharmacokinetic
PT	Preferred Term
RET	rearranged during transfection
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical safety
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SPM	second primary malignancy
SRS	stereotactic radiosurgery
TKI	tyrosine kinase inhibitor
TNM	cancer staging system : primary tumor (T), regional lymph nodes (N), distant metastasis (M)
UICC	Union Internationale Contre le Cancer
ULN	upper limit of normal
V/F	apparent volume of distribution
WBRT	whole brain radiotherapy

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 24 November 2023 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of indication to include the use of Alecensa as monotherapy in adult patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) as adjuvant treatment following tumour resection, based on final results from study BO40336 (ALINA), a randomized, active controlled, multicenter, open-label, Phase III study designed to evaluate the efficacy and safety of alectinib compared with platinum-based chemotherapy in the adjuvant setting in patients with completely resected Stage IB (tumors ≥4 cm) to Stage IIIA ALK-positive NSCLC. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and to introduce editorial changes to the PI. As part of the application, the MAH is requesting a 1-year extension of the market protection.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0359/2018 on the granting of a (product-specific) waiver covering the condition "Treatment of non-small cell lung cancer".

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson

Timetable	Actual dates
Submission date	24 November 2023
Start of procedure:	23 December 2023
CHMP Rapporteur Assessment Report	16 February 2024
PRAC Rapporteur Assessment Report	23 February 2024
PRAC members comments	28 February 2024
PRAC Outcome	7 March 2024
CHMP members comments	11 March 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	14 March 2024
Request for supplementary information (RSI)	21 March 2024
CHMP Rapporteur Assessment Report	11 April 2024
PRAC Rapporteur Assessment Report	10 April 2024
CHMP members comments	n/a
PRAC members comments	n/a
Updated CHMP Rapporteur Assessment Report	18 April 2024
Updated PRAC Rapporteur Assessment Report	18 April 2024
Opinion	25 April 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

State the claimed the therapeutic indication

Alecensa as monotherapy is indicated as adjuvant treatment following tumour resection for adult patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC).

Epidemiology

ALK fusions are found in approximately 4–5% of patients with NSCLC. ALK-positive NSCLCs are generally associated with young age, never- or light-smoking history, adenocarcinoma histology, and are associated with a high rate of brain metastases (~50-60% of patients over the course of their disease) (Zhang et al. 2016; Johung et al. 2016, Aldea et al 2020).

Management

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, and immunotherapy is generally not recommended in patients with ALK-positive disease. Therefore, for patients with resected ALK-positive NSCLC, adjuvant chemotherapy is still the standard of care (NCCN 2023, ESMO 2021).

Data from historical adjuvant studies showed that adjuvant chemotherapy provides limited benefit in the all-comer population with modest benefit for Stage IB patients (Pignon et al 2008), and no survival advantage specifically in Stage IB patients with tumours < 4 cm (Strauss et al. 2011). Since no benefit has been demonstrated with chemotherapy treatment, surgical resection without any adjuvant therapy remains the standard of care in this population (NCCN 2023, ESMO 2021). The long-term outcome nevertheless remains poor, with approximately 40-46% of patients suffering from cancer recurrence within the first 5 years after initial diagnosis, and only 60-73% remaining alive at 5 years (Chansky et al. 2017).

2.1.2. About the product

Alectinib (also known as Alecensa, RO5424802, AF802, or CH5424802) is a tyrosine kinase inhibitor (TKI) that targets anaplastic lymphoma kinase (ALK) and rearranged during transfection (RET), thereby inhibiting intracellular signaling pathways involved in tumor cell proliferation and survival. Alectinib promotes cancer cell death by restoring apoptosis and inhibiting tumor cell growth and proliferation.

Alectinib was first approved in Japan for the treatment of ALK−positive unresectable, recurrent or advanced non-small cell lung cancer (NSCLC), and then globally (including Japan) for the treatment of patients with ALK-positive, locally advanced or metastatic NSCLC (mNSCLC) who have progressed on or are intolerant to crizotinib therapy. Subsequently, alectinib was also approved globally in the first-line locally advanced or metastatic NSCLC setting.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Compliant.

2.1.4. General comments on compliance with GLP and GCP

The Marketing Authorisation Holder (MAH), Roche Registration GmbH confirms that all clinical trials carried out outside the European Union meet the ethical requirements of the EU Clinical Trial Directive [2001/20/EC]. For studies conducted in the EU/EEA countries, the investigator have ensured compliance with the EU Clinical Trial Directive [2001/20/EC].

For studies conducted in the USA or under US IND, the investigator have also ensured adherence to the basic principles of "Good Clinical Practice" as outlined in the current version of 21 CFR, subchapter D, part 312, "Responsibilities of Sponsors and Investigators", part 50, "Protection of Human Subjects", and part 56, "Institutional Review Boards".

In other countries where "Guideline for Good Clinical Practice" exists Roche and the investigators strictly ensure adherence to the stated provisions.

2.2. Non-clinical aspects

2.2.1. Introduction

No new non-clinical data have been submitted in this application. The proposed new indication for alectinib is the adjuvant treatment following tumour resection in patients with ALK-positive NSCLC, which involves continuous treatment with alectinib for 2 years.

2.2.2. Toxicology

Repeat dose toxicity

Alectinib has been tested in sub-chronic Good Laboratory Practice (GLP) repeat-dose toxicity studies of up to 13 weeks treatment duration in rat and cynomolgus monkey. No chronic toxicity studies of 26 weeks in rat and 39 weeks in monkey have been conducted.

Carcinogenicity

No carcinogenicity studies have been conducted to date with alectinib.

The risk for second primary tumors under alectinib treatment has been assessed based on:

1. *The available repeat-dose toxicity data with alectinib of up to 13 weeks duration in rat and cynomolgus monkey*

Administration of alectinib for up to 13 weeks was associated with minimal to slight extension of the proliferative zone of the mucosa of the stomach and intestine in both rat and cynomolgus monkey. This change was accompanied by concomitant degeneration and inflammation of the mucosa in the rat. In addition, minimal bile duct proliferation was reported in the 13-week studies in both species.

The extension of the proliferative zone of the stomach and intestine in the toxicity studies with alectinib is considered a consequence of an accelerated cell turnover. The presence of degeneration of the glandular epithelium as well as desquamation/disarrangement of the epithelium accompanied by inflammatory cell infiltration in the stomach and intestine of rats indicates that the extension of the proliferative zone of the epithelium is a reactive change. Although no obvious degeneration or inflammation was noted in the studies in cynomolgus monkey, the minimal extension of the proliferative zone in the mucosa is considered to be consistent with an accelerated cell turnover and regeneration. No exacerbation of the severity of the extension of the proliferative zone was observed in the 13-week toxicity studies compared with the 4-week toxicity studies in both species. In addition, this finding was completely reversible after the recovery period in the cynomolgus monkey studies, and showed tendency for recovery in the rat studies. Due to its minor severity, the absence of

exacerbation over time and its reversibility, no progression of this finding is expected in longer duration studies.

Bile epithelium proliferation (bile duct hyperplasia) is a common finding in aging rats but can also be a response to drug administration. The initial response is a damage to the biliary epithelium followed by proliferation of the bile ducts In the studies performed with alectinib, the bile duct proliferation was of minimal severity, only observed after 13 weeks of treatment, and completely reversible. It is known that many chemicals that induce substantial bile duct proliferation fail to cause the formation of bile duct neoplasms. Due to the minor severity of this finding in the 13-week studies, a progression to neoplasms in a 2-year study is considered very unlikely.

2. The aneugenicity of alectinib and risk to cause or contribute to tumor promotion

Alectinib does not induce gene mutations or structural chromosome damage but causes micronuclei in proliferating cells via an aneugenic mode of action. In the two in vivo micronucleus studies, a slight increase of micronucleus frequency was observed at $\geq$500 mg/kg/day, while 200 mg/kg/day is considered the no observed effect level (NOEL). The plasma exposure at the NOEL (C_{max} 1850 ng/mL; $AUC_{0\text{-}24h}$ 36700 ng•h/mL) provides a 2–3-fold safety margin to the human plasma exposure (based on geometric means at steady state for $C_{ss,max}$ [665 ng/mL] and $AUC_{ss,24h}$ [14900 ng•h/mL]).

There is consensus in the scientific community that aneugenic pathways do not play a primary causative role in human carcinogenicity. Also, it is now widely accepted that the shape of the dose-response curve of aneugens (in contrast to most mutagens and clastogens) is non-linear and that aneugenic agents exert their genotoxicity through an indirect mode of action. DNA damage occurs only above a so-called "threshold", once the primary protein targets of the aneugens are saturated/inhibited to a sufficient extent. Exposures below the threshold are therefore deemed safe.

3. Any additional potential factors such as hormonal perturbation following treatment with alectinib

The nonclinical data with alectinib do not indicate any undue hormonal perturbations that could give rise to tumor promotion or progression. Similarly, the clinical safety data with alectinib do not indicate such findings.

4. The long-term clinical safety data on tumorigenicity with alectinib treatment

No concern has arisen with regard to secondary primary malignancies (SPM) in the clinical use of alectinib. The incidence of SPM in patients treated with alectinib in the advanced ALK-positive NSCLC setting as well as in the ALINA adjuvant trial was within the range of background incidence of SPM in the NSCLC population from epidemiological sources.

Developmental and reproduction toxicity

Preliminary embryo-fetal development (pEFD) GLP studies with alectinib in rats and rabbits have been conducted and reviewed as part of the initial marketing application in accordance with the ICH S9 guideline. Based on these studies and on the aneugenic potential of alectinib, there is a continued need for contraception for patients of childbearing potential during exposure to alectinib.

GLP pEFD studies in rats and rabbits conducted with alectinib revealed embryo lethality and dysmorphogenesis at clinically relevant exposure levels in both species. No main embryo-fetal development (EFD) studies were considered necessary since the preliminary studies had already identified a clear developmental hazard.

A requirement for PPND and female fertility studies for alectinib is not warranted. A warning and precaution in the product information is in place for embryo-fetal toxicity, which requires highly

effective contraception methods during exposure to alectinib. It has been reported in the literature that alectinib is excreted in human breast milk. The product information for alectinib (section 4.6 of the SmPC) advises mothers against breastfeeding their infant. In view of the general and developmental toxicity profile of alectinib, this recommendation is unlikely to change. Therefore, a PPND study is not considered to be required for the purpose of detecting possible effects on the breastfed infant. While no dedicated fertility studies have been conducted, reproductive organs were examined in the repeat-dose studies of up to 13-week duration and no test article-related adverse findings were observed.

2.2.3. Ecotoxicity/environmental risk assessment

The current Environmental Risk Assessment (ERA) for ALECENSA for anaplastic-lymphoma-kinase-positive (ALK+) advanced non-small-cell lung cancer (NSCLC) patients previously treated with crizotinib, was prepared January 14, 2016. In this ERA, the maximum theoretical use of Alectinib was refined based on the epidemiologically substantiated prevalence of ALK+ NSCLC, and comprising all expected cases of ALK+ NSCLC, not only the ones previously treated with crizotinib.

2.2.4. Discussion on non-clinical aspects

No further non-clinical studies were submitted to support this application for an adjuvant indication in NSCLC, based on the ICH S9 Q&A which recommends that the need for additional studies (e.g., carcinogenicity, a complete program on reproductive and developmental toxicity) and their timing can be addressed on a case-by-case basis, taking into account the totality of preclinical and clinical safety data, cure rate and expected time to recurrence. As outlined in the ICH S9 Q&A guidance, ICH S9 should be used as the "starting point for drugs used in an adjuvant or neo-adjuvant setting even when there is a lack of detectable residual disease. Data generated in patients (e.g., when the initial program was in a refractory late stage disease) should be considered and may be used to abbreviate the nonclinical program. In cases in which cure rate and recurrence rate are less defined the need for additional studies (e.g., carcinogenicity, a complete program on reproductive and developmental toxicity) and their timing can be addressed on a case-by-case basis, taking into account the totality of preclinical and clinical safety data, cure rate and expected time to recurrence."

The available and emerging clinical data is considered to provide the most relevant safety information for an assessment of alectinib's general toxicity profile. As indicated in the ICH S9 Q&A guidance, clinical safety data generated in the patient population for the approved indication are most meaningful and relevant to inform the safety plan for the patient population in the ajuvant indication. The review of cumulative safety data from the pivotal ALEX trial (BO28984), including data of up to 5 years of treatment, did not identify any additional safety concerns originating from long-term alectinib therapy. Concerning chronic toxicity it is agreed that the available nonclinical data and clinical experience can justify that such studies are not warranted

The existing non-clinical data were further discussed and they are not suggestive of a carcinogenic risk. While the reasoning is agreed, it should be pointed out that for making a weighed evidence assessment of carcinogenic risk (as described in ICH S1B(R1)), data from studies on chronic toxicity are considered pivotal. The available non-clinical data are therefore not sufficient for such approach. Clinical data which have not shown any concern on the development of secondary primary malignancies were also taken into account. While this is reassuring, these data are not considered sensitive to detect a carcinogenic risk over a longer period of time. Therefore, the decision on the need for carcinogenicity studies depends very much on the expectation of survival in the patient population targeted by the adjuvant indication. The MAH expects the median overall survival (OS) of alectinib in the adjuvant setting to exceed 5 years. In so, data from a carcinogenicity program are considered to

add information of value. Since a relevant improvement in DFS has been demonstrated and available data are not suggestive of a carcinogenic potential, it is agreed that these data can be provided post-approval. The MAH will therefore perform a carcinogenicity program in accordance with ICHS1B, including a 26 weeks oral gavage toxicity and toxicokinetic study in. CByB6F1-Tg(HRAS)2Jic (rasH2 tg/wt, model 1178) mouse as well as a 104-Week Rat carcinogenicity study to further address the missing information of carcinogenicity as a post authorization commitment. Final results will be provided by Q1 2027 and Q4 2028 respectively. The RMP has been updated to include "carcinogenicity" as missing information in the list of safety concerns and to include the 2 post authorisation studies as additional pharmacovigilance activities. Concerning developmental and reproductive toxicity, based on the clear findings on embryofetal toxicity and the current recommendations in the SmPC, it is agreed that a PPND study would not add value. In absence of findings on reproductive organs in toxicity studies, it is also agreed that a fertility study will not be warranted.

Impurities were evaluated according to ICH M7 at the time of the initial MAA.

The existing ERA, as described in section 2.2.3, covers the potential environmental risks deriving from applications intended for the treatment of all potential ALK+ NSCLC patients. Therefore, no new updated environmental risk assessment is needed for the adjuvant indication.

2.2.5. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted in this application. Based on the previously submitted non-clinical safety data and the available clinical safety data with alectinib, the current non-clinical data package supports the proposed indication for alectinib in the adjuvant setting. However, the MAH will perform 2 new non-clinical studies, a 6-month transgenic TgHras2 mouse study and a 2-year rat carcinogenicity.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Number	*Study Design*	*Population*	*Total No. of PK-evaluable Patients*	*Endpoints*	*Status*
BO40336 (ALINA)	randomized, active controlled, multicenter, open-label, Phase III study	Stage IB-IIIA ALK-positive NSCLC after (or following) surgical resection	124	Efficacy and Safety	Ongoing

ALK=Anaplastic Lymphoma Kinase; NSCLC=Non-Small Cell Lung Cancer

For additional details of the study design, please see 2.4 Clinical Efficacy and 2.5 Clinical Safety sections.

2.3.2. Pharmacokinetics

A total of 124 patients who had at least one Pharmacokinetic (PK) measurable sample post-dose for alectinib and M4 were included in the PK analysis (PK cutoff date: 28 February 2023). Sparse PK samples were collected at predose (Weeks 3, 6, 9, 12, 24, 36, 48, 60, 72, 84 and 96) for all the patients enrolled within the alectinib arm. Additionally, for the first 6 Japanese patients enrolled in the study, intensive PK collection was performed during Week 3 visit (predose, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours; 12-hour collection was optional).

PK results from ALINA were presented as descriptive summaries of the observed PK data of alectinib and the metabolite M4 (see section 2.3.2.1), and as a population PK analysis (see section 2.3.2.2).

2.3.2.1. Bioanalysis

Bioanalytical methods, validation parameters, and method performance were presented in the initial application, with additional updates as described below:

For the simultaneous measurement of both alectinib and the M4 metabolite in human plasma for ALINA, the LC-MS/MS method developed and validated at Q2 Solutions (formerly Quintiles, Ithaca, US) was used. Alectinib and M4 stability at nominal -70°C was updated from 552 days reported initially to 1362 days (data not shown). To enable local analysis of human plasma samples collected in China from ALINA, the LC-MS/MS method for alectinib and M4 was transferred, slightly modified (lower plasma volume and more sensitive mass spectrometer), and validated at Q2 Solutions Beijing, China.

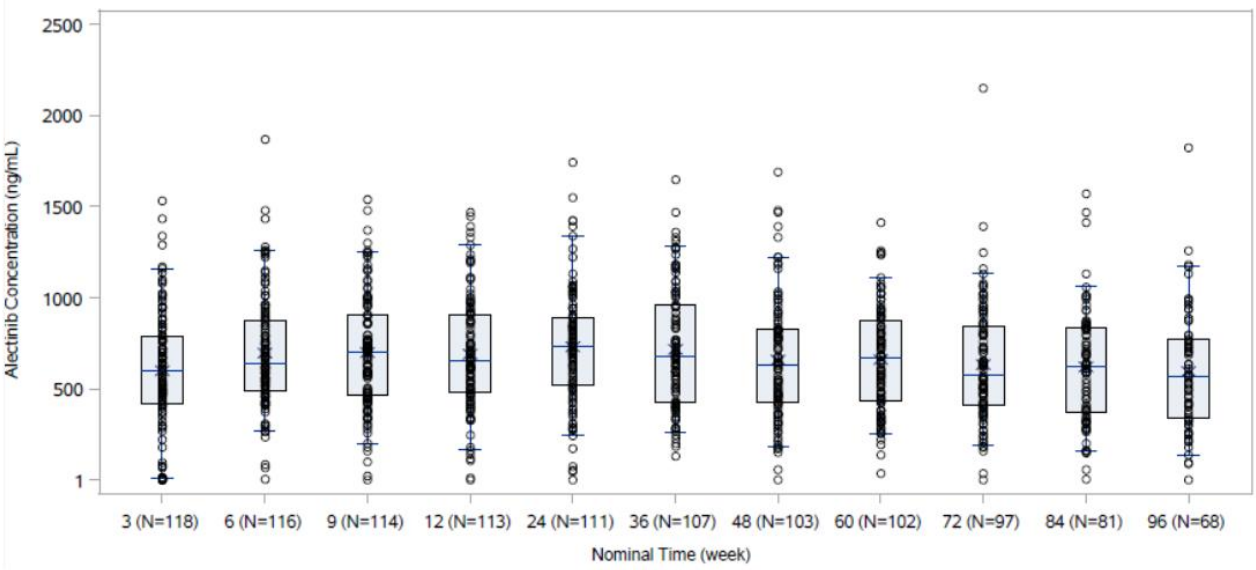
The two methods validated for alectinib and the M4 metabolite in human plasma at Q2 Solutions US and China were compared by cross-validation. No significant bias was seen in Q2 Solutions Beijing results when compared with the concentrations observed at Q2 Solutions US for either alectinib or the M4 metabolite. The results show that the two LC-MS/MS assays are comparable and will produce consistent results in the study samples analysed at the two different laboratories (data not shown).

Validation procedures and the sample analysis acceptance criteria were followed according to each laboratory's Standard Operating Procedures, which are based on internationally accepted guidance and local regulations.

2.3.2.2. Descriptive PK

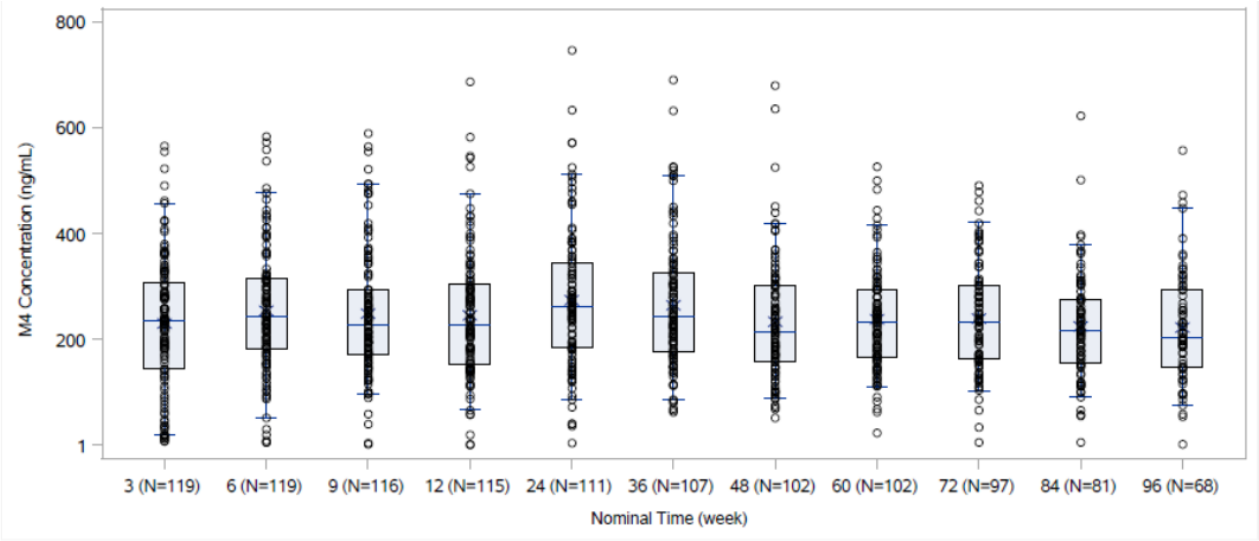
Observed geometric mean alectinib pre-dose plasma concentration at the end of a dosing interval (Ctrough) across visits ranged from 382-639 ng/mL and was associated with a moderate to high variability (geometric mean CV%) ranging from 54.1% to 276.2% across visits. Geometric mean M4 observed predose plasma concentrations (Ctrough) across visits ranged from 178-238 ng/mL and were associated with a moderate variability (geometric mean CV%) ranging from 49.7% to 111.7% across visits. Results show that steady state predose (Ctrough) concentrations within this study were comparable across the different visits for both alectinib and M4 plasma concentrations.

A box plot showing the observed predose (Ctrough) concentration data by visit for alectinib and M4 is provided in Figure 1 and Figure 2, respectively.



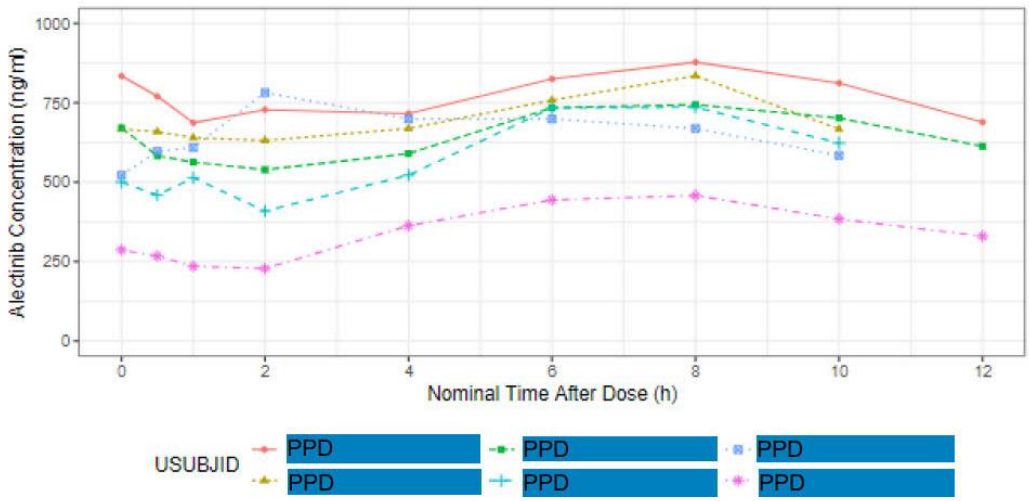
Note: The boxplot represents the distribution of the model predicted data. Solid line in the center represents the median, solid line at the bottom is the 25th percentile (Q1), solid line on top is 75th percentile (Q3) while the boxes indicate the inter-quartile range (IQR; Q3-Q1) and the whiskers represent 1.5*IQR.
N=number of subjects

Figure 1. Observed predose (Ctrough) alectinib plasma concentration



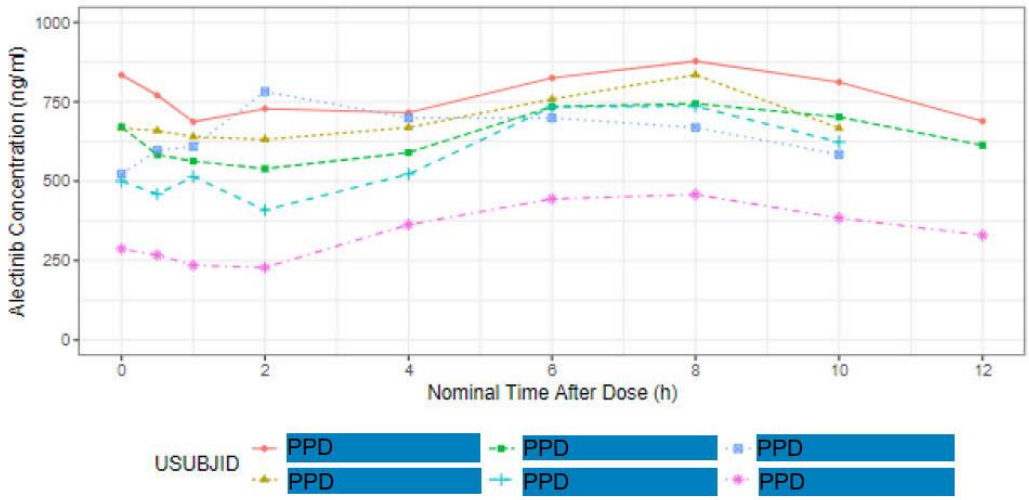
Note: The boxplot represents the distribution of the model predicted data. Solid line in the center represents the median, solid line at the bottom is the 25th percentile (Q1), solid line on top is 75th percentile (Q3) while the boxes indicate the inter-quartile range (IQR; Q3-Q1) and the whiskers represent 1.5*IQR.
N=number of subjects

Figure 2. Observed predose (ctrough) M4 plasma concentration



Lines and symbols = observations.

Figure 3 displays the alectinib concentration-time profiles for the six Japanese subjects with rich PK collected at Week 3.



Lines and symbols = observations.

Figure 3. Rich alectinib concentration-time profiles from six Japanese participants (Week 3)

2.3.2.3. Population PK analyses

A population PK analysis was submitted with this application.

2.3.2.3.1. Objectives

The objectives of the population PK analyses of Phase III ALINA study in patients with resected Stage IB-IIIA ALK positive NSCLC, who received alectinib 600mg BID were to:

• Describe the PK of alectinib and its major active metabolite M4 in patients with resected Stage IB-IIIA ALK-positive NSCLC in ALINA.

• Confirm the effects of covariates which contribute significantly to the between-patient variability in PK parameters of alectinib and M4 in patients with resected Stage IB-IIIA ALK-positive NSCLC in ALINA.

• Determine individual estimates for derived secondary PK parameters for exposure-efficacy and -safety analyses and for summary statistics.

2.3.2.3.2. Data

The population PK analysis was conducted on the ALINA PK population, defined as all patients who received alectinib and have at least one measurable PK observation post their first dose. Pre-dose PK sampling was collected (baseline, and Weeks 3, 6, 9, 12, 24, 36, 48, 60, 72, 84, and 96) in all subjects. Rich PK at Week 3 was also collected in six Japanese subjects. In total the population PK datasets consisted of 1170 alectinib concentrations and 1173 M4 concentrations from 124 subjects.

Alectinib and M4 below the lower limit of quantification (BLQ) data were omitted from analysis according to the M1 methodology. A total of 154 alectinib and 151 M4 observations were excluded from the population PK datasets. The majority of these observations were excluded due to pre-first

dose BLQ samples. Post-dose BLQ samples accounted for <2% of all observations. A total of 7 alectinib and 11 M4 observations were excluded as outliers, defined as an absolute conditional weighted residuals (CWRES) of >5. As note, there were four subjects completely excluded from the analysis as they did not have any quantifiable PK collected.

The summary of subject demographics are provided in Table 1 and Table 2.

Table 1. Summary of continuous demographics at baseline

	Age (years)	Weight (kg)	SCRT (umol/L)	CRCL (ml/min)	ALT (U/L)	AST (U/L)	TBIL (umol/L)
N	124	124	124	124	124	124	124
Missing	0	0	0	0	0	0	0
Mean	53.3	68.8	68.9	99.5	23.7	22.7	11.2
SD	12.3	15.9	14.8	30.7	17	9.6	6.4
CV %	23	23.1	21.5	30.8	72	42.4	57
Median	54	65.6	68	94.4	20	20.2	9.8
Min	26	40.5	43.3	48.4	6	11	3.4
Max	80	120	115	264	128	78	39.1

N = number of subjects, SD = standard deviation, CV = coefficient of variation, Min = minimum, Max = maximum, SCRT = serum creatinine, CRCL = creatinine clearance, ALT = alanine aminotransferase, AST = aspartate aminotransferase, TBIL = total bilirubin.

Table 2. Summary of categorical demographics at baseline

Sex	Race	Chinese Race	Ethnicity	Smoking History	Cancer Stage	ECOG Score	Hepatic Impairment	Renal Impairment
Female: 72 (58.1%)	White: 53 (42.7%)	Non-Chinese: 99 (79.8%)	Non-Hispanic or Latino: 121 (97.6%)	Never: 82 (66.1%)	Stage IB: 13 (10.5%)	0: 71 (57.3%)	Normal: 106 (85.5%)	Normal: 69 (55.6%)
Male: 52 (41.9%)	Black or African American: 1 (0.8%)	Chinese: 25 (20.2%)	Hispanic or Latino: 1 (0.8%)	Previous: 38 (30.6%)	Stage II: 44 (35.5%)	1: 53 (42.7%)	Mild: 15 (12.1%)	Mild: 53 (42.7%)
	Asian: 68 (54.8%)		Not-Reported: 2 (1.6%)	Current: 4 (3.2%)	Stage IIIA: 67 (54%)		Moderate: 3 (2.4%)	Moderate: 2 (1.6%)
	Unknown: 2 (1.6%)							

ECOG = Eastern Cooperative Oncology Group, See Appendix C for definitions of hepatic and renal impairment groups. Chinese race defined by country code including China (n=22 subjects), Taiwan (n=3 subjects) and Hong Kong (n=0 subjects).

2.3.2.3.3. Methods

The previously established population PK models for alectinib and M4 were fitted to the PK data in patients with resected Stage IB-IIIA ALK-positive NSCLC in ALINA who received alectinib 600mg BID, with parameters fixed to the final estimates from the previously established population PK model (MAXEVAL=0).

The following techniques were used to evaluate if the previously established models adequately describe the alectinib and M4 PK data:

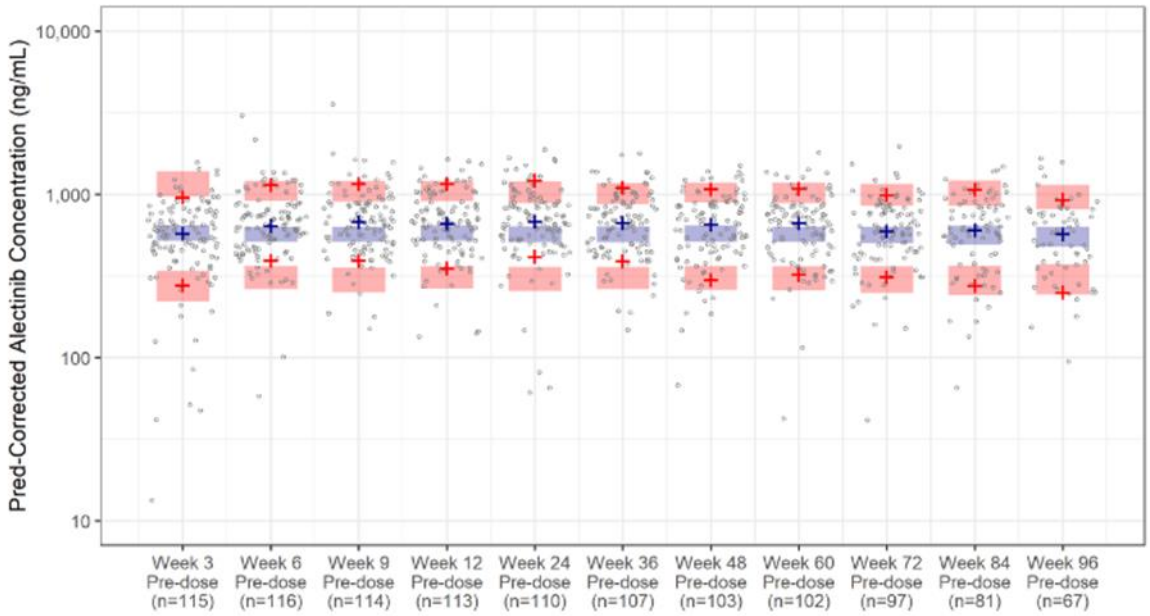
- Standard goodness-of-fit plots
- Prediction corrected visual predictive checks (pcVPCs) were performed to determine if the model's simulation characteristics were adequate. The pcVPCs were performed by simulating 1000 replicates of the concentration-time data from the posterior distribution of the models to compute the 95% confidence interval (CI) around the 10th, 50th, and 90th prediction percentiles (80% prediction interval). The observed data was overlaid on the simulated prediction interval together with the 10th, 50th, and 90th percentiles computed from the observed data.
- The influence of categorical and continuous covariates on alectinib and M4 PK were evaluated by graphical review. Boxplots of random effects vs. categorical covariates and scatter plots of random effects vs. continuous covariates were constructed to identify trends

2.3.2.3.4. Results

To evaluate the predictive performance of the model, a pcVPCs were conducted (Figure 4 and Figure 5).

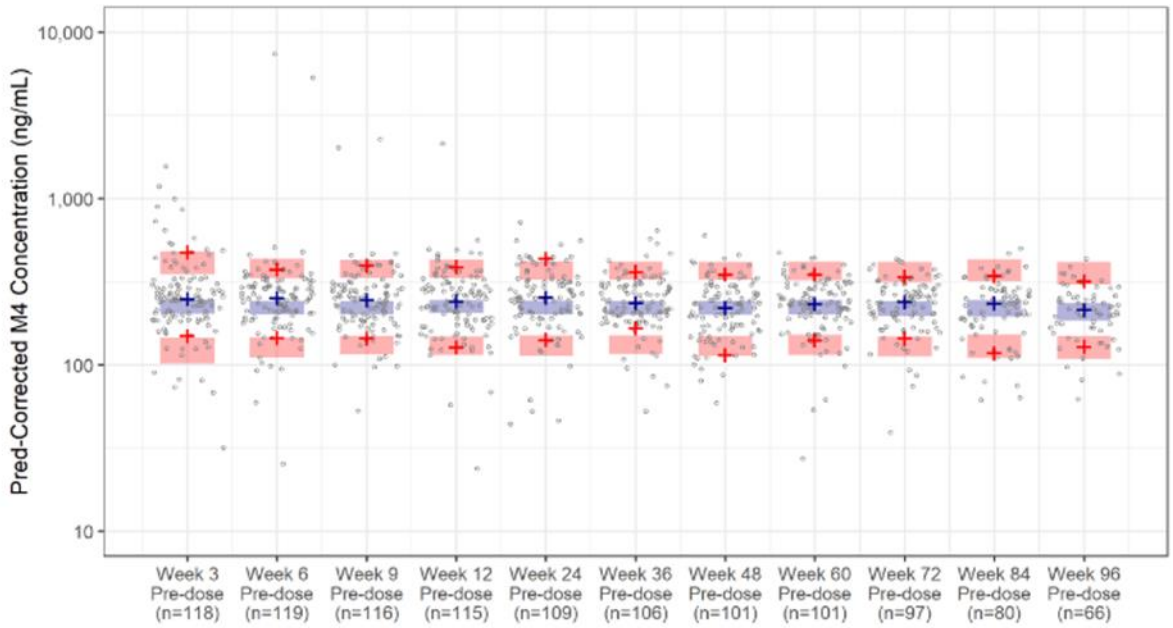
For alectinib, individual estimates of shrinkage for CL/F, apparent volume of distribution (V/F), first-order absorption rate constant (KA), and duration of zero-order input into the first compartment (D1) were 5.8%, 14.1%, 88.6%, and 82.0%, respectively.

For M4, individual estimates of shrinkage for CL/F, V/F, and first-order formation rate constant (Kform) were 13.1%, 35.7%, and 79.8%, respectively.



Circles = observed data, red crosses = observed 10th & 90th percentiles, blue crosses = observed median, red shaded areas = 95% confidence intervals for 10th & 90th percentiles of the simulated data, blue shaded areas = 95% confidence intervals for 50th percentiles of the simulated data. Log-y axis. Note: y-axis truncated between 10 - 10,000 ng/mL to allow for visualization. Non-truncated pcVPC displayed in Appendix H.

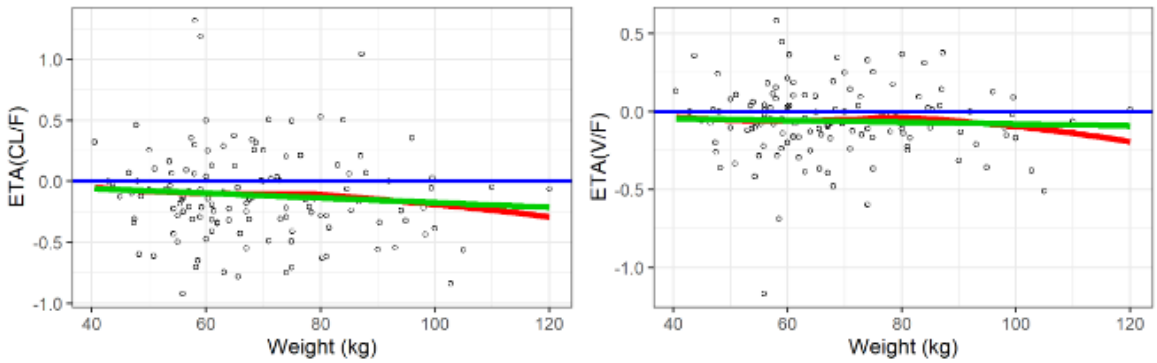
Figure 4. pcVPC (Alectinib)



Circles = observed data, red crosses = observed 10th & 90th percentiles, blue crosses = observed median, red shaded areas = 95% confidence intervals for 10th & 90th percentiles of the simulated data, blue shaded areas = 95% confidence intervals for 50th percentiles of the simulated data. Log-y axis. Note: y-axis truncated between 10 - 10,000 ng/mL to allow for visualization. Non-truncated pcVPC displayed in Appendix O.

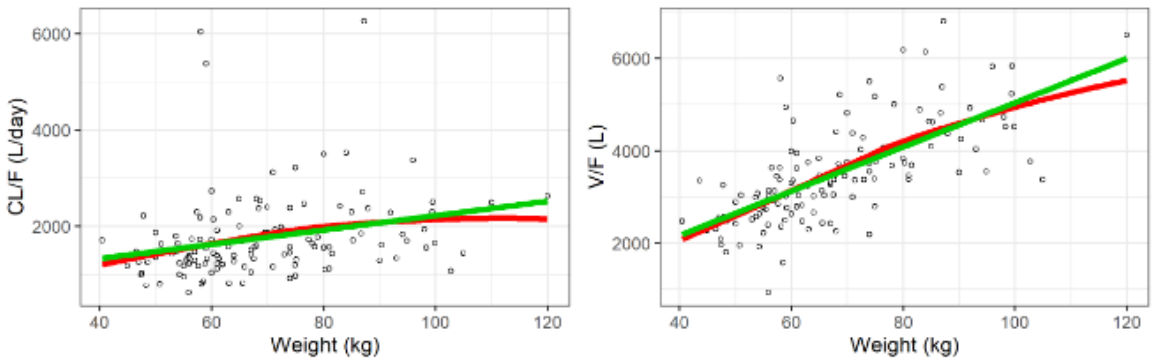
Figure 5. pcVPC (M4)

Diagnostic plots of BSV random effects versus covariates confirmed that WT is the only significant covariate for alectinib and M4 (alectinib: Figure 6 and Figure 7, M4: Figure 8 and Figure 9), as identified in the previous population PK model. All other covariates investigated were confirmed to have no evident effect on the PK of alectinib or M4 (data not shown).



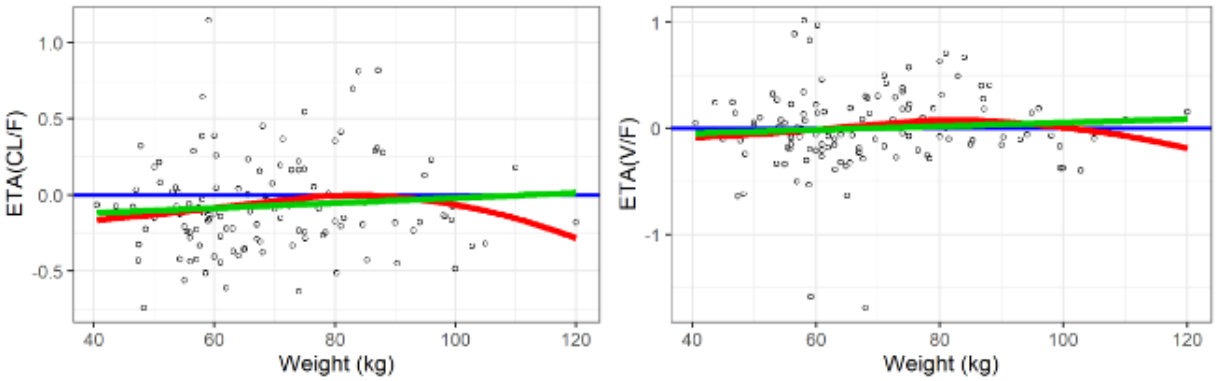
Solid red line = loess smooth, solid green line = linear regression.

Figure 6: Relationship between body weight and ETA for CL/F and V/F (Alectinib)



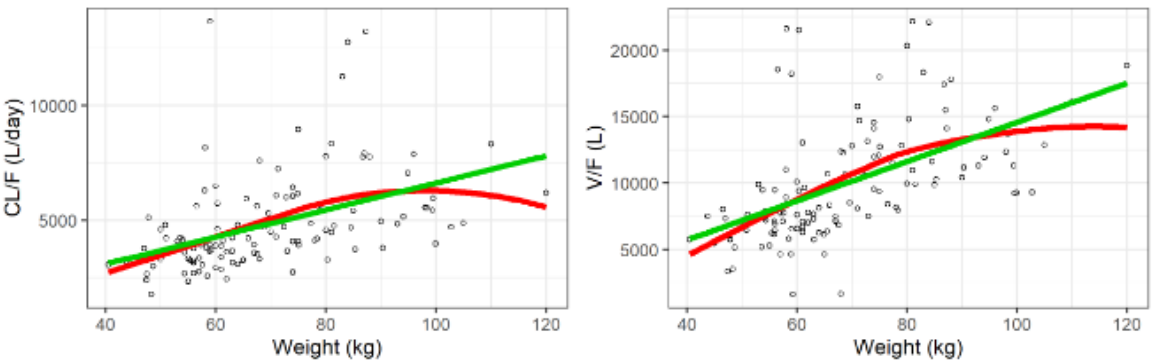
Solid red line = loess smooth, solid green line = linear regression.

Figure 7: Relationship between body weight and the individual PK parameters (Alectinib)



Solid red line = loess smooth, solid green line = linear regression.

Figure 8: Relationship between body weight and ETA for CL/F and V/F (M4)



Solid red line = loess smooth, green line = linear regression.

Figure 9: Relationship between body weight and the individual PK parameters (M4)

2.3.3. Pharmacodynamics

Pharmacodynamic data were not collected for ALINA.

2.3.4. PK/PD modelling

PK/PD modelling was applied on clinical data from ALINA. Exposure-response analyses were conducted both for safety and efficacy endpoints, as described below.

2.3.4.1. Exposure-safety relationship

Exposure-safety analyses demonstrated that there was no significant relationship between total alectinib and M4 exposure and the occurrence of SAEs or Grade ≥3 AEs at the dose of alectinib 600 mg BID. These results are supportive of the well-tolerated safety profile for alectinib 600 mg BID (data not shown).

2.3.4.2. Exposure-efficacy relationship

Cox proportional-hazards (CPH) analysis demonstrated that no significant exposure-efficacy relationship was identified for the primary efficacy endpoint DFS by investigator assessment following alectinib 600 mg BID in the ALINA study (data not shown). This result indicates that the alectinib efficacy benefit is similar across the PK exposure range following a dose of alectinib 600 mg BID, and is therefore, supportive of 600 mg BID alectinib for patients with Stage IB-IIIA ALK-positive NSCLC after (or following) surgical resection.

2.3.5. Discussion on clinical pharmacology

The pharmacokinetics of alectinib and its major metabolite (M4) have been characterised previously in ALK-positive NSCLC patients and healthy subjects (see Alecensa MAA EPAR and Alecensa II/01 EPAR).

In this application, additional information on the clinical pharmacology of alectinib was obtained by including results from the Phase III study ALINA (BO40336). PK analyses from the ALINA study were used to describe PK in the target population of the adjuvant indication.

Bioanalysis: The analytical method used to analyse samples from ALINA study was partly already assessed and found acceptable in the initial marketing authorisation procedure. Long-term stability has been updated to 1362 days at -70°C. The analytical method developed and validated at Q2 Solutions (formerly Quintiles) Ithaca, USA was transferred, slightly modified, and validated at Q2 Solutions Beijing, China. The two methods were compared by cross-validation and the results from both laboratories met acceptance criteria.

Descriptive PK: The observed trough concentrations of alectinib and M4 were summarised as box plots stratified by each visit. This is considered a reasonable presentation of the data.

The current SmPC for Alecensa states that the mean (coefficient of variation %) Cmin at steady state is 572 ng/mL (47.8%) and 222 ng/mL (46.6%) for alectinib and M4, respectively in the already approved indication (ALK-positive NSCLC patients). The PK Ctrough results from ALINA is in overall agreement with the PK data in the previous target population.

The trough concentrations appear to be overall stable over time. The first time-point with PK data is week 3 at which point all subjects are expected to be at steady state.

Population PK: The objectives of the PK analyses are considered acceptable. The dataset used for the analysis included 1170 alectinib concentrations and 1173 M4 concentrations from 124 subjects which is a reasonable database given the objectives. It should be noted that most samples are trough samples and it may be difficult to draw conclusions regarding the absorption phase but this is still considered

acceptable given the role of PopPK in the current procedure. The data exclusions are considered acceptable. The data exclusions were mainly due to pre-dose samples below the lower limit of quantification. Apart from this, there were a few outliers and post-dose data below the lower limit of quantification. The covariate distributions of continuous and categorical covariates appear reasonable.

The methods are considered overall acceptable. A previous model of alectinib and M4 was used with fixed parameter estimates (MAXEVAL=0) approach which is considered acceptable. Since the dataset mainly includes trough samples, it can be advantageous to rely on a previous model since parameters which are not informed by trough samples (such as absorption-related parameters) can be biased and/or difficult to interpret for a model developed only on trough samples. It would be important to demonstrate that the previous model give acceptable description of the observed data according to model diagnostics. Relevant model diagnostic tools were used to assess the ability of the model to describe the observed data. The covariate analysis was based on a graphical exploration of random effects (etas) plotted versus covariates. This method is sensitive to the eta shrinkage. The eta shrinkages were acceptable for CL/F and V/F terms (see results section for further details).

The results were presented mainly in terms of pcVPCs to demonstrate that the model can describe the observed data, and random effects vs covariate plots were provided as a form of covariate analysis. Overall, it can be seen that the previously established model described the observed alectinib and M4 concentrations adequately with an even distribution of observations above and below the 10th and 90th prediction intervals. It can also be seen that the simulated median values largely agree with the observed alectinib and M4 data. The predictive performance of the population PK model for alectinib M4 was considered to be satisfactory and therefore qualified for its use for simulation.

Other standard goodness-of-fit plots were also provided in the PopPK report and they did not indicate any major model misspecification.

The ETA shrinkages for CL/F and V/F terms were in an overall acceptable range. The shrinkages were below 20% apart from V/F for M4 where shrinkage was ~35%. 35% is borderline too high for the covariate analysis to be completely reliable. However, since only one parameter of potential interest had shrinkage over 20% and the PopPK analysis in general had limited impact for the overall benefit/risk assessment, this issue was not pursued further.

Shrinkage was considerably higher for absorption related parameters but this is not of primary interest in the current procedure and is reasonable given the sparse PK sampling design. Hence, this approach for evaluating covariates is considered acceptable.

The conclusions that body weight is the only potentially clinically relevant covariate is accepted. This is in line with the previous PopPK model based on adult patients with anaplastic lymphoma kinase (ALK)-positive advanced NSCLC.

Overall, the PK analyses (descriptive PK analysis and PopPK analysis) support the conclusion that PK is similar between the current target population (adjuvant treatment following tumour resection for adult patients with ALK-positive non-small cell lung cancer) and the previous target population (adult patients with ALK-positive advanced non-small cell lung cancer).

PK/PD modelling: Exposure-response analyses were performed based on efficacy and safety data. The exposure-response analyses are considered supportive only to the clinical efficacy and safety analyses described in the corresponding sections of this AR. The impact on the overall benefit-risk assessment is low. Reasonable efficacy-, safety- and exposure variables/endpoints were included in the exposure-response analyses.

2.3.6. Conclusions on clinical pharmacology

The PK of alectinib and its major metabolite M4 in the target population is well described. The exposure-response analyses of efficacy and safety endpoints are considered acceptable.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

The alectinib 600 mg BID dosing regimen was selected for evaluation within ALINA based on previous experience within the mNSCLC indication. The approved alectinib dosing regimen of 600 mg orally BID within the mNSCLC indications were originally supported by clinical safety, efficacy and PK data from Phase II Studies NP28761 and NP28673, and the Phase III global Study BO28984 (ALEX).

2.4.2. Main study

Pivotal study BO40336 (ALINA)

Overview

ALINA is a Phase III, global, multicenter, open-label, randomized superiority study designed to investigate the efficacy and safety of alectinib compared with platinum-based chemotherapy in the adjuvant setting in patients with completely resected Stage IB-IIIA ALK-positive NSCLC (**Figure 10**). The primary and secondary efficacy endpoints of the study are INV-DFS and OS, respectively.

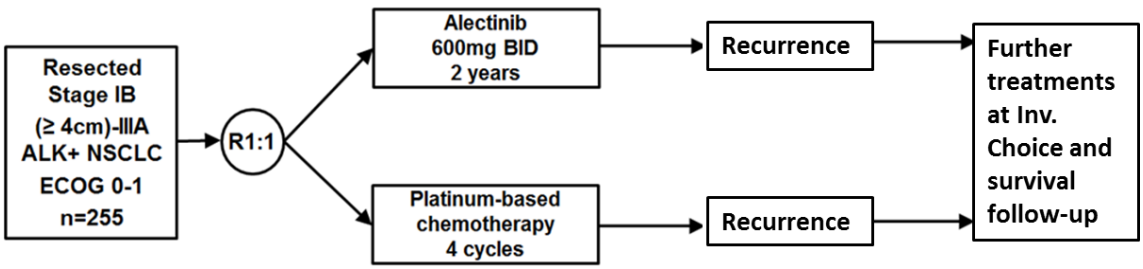


Figure 10: Overview of pivotal study B040336

Methods

Study participants

Patients with completely resected Stage IB-IIIA ALK-positive NSCLC were enrolled in this study. Key criteria relevant to efficacy are summarized below.

Key Inclusion Criteria

Patients must have met the following criteria for inclusion in the study:

- Age ≥ 18

- Complete resection of histologically confirmed Stage IB (tumor ≥ 4 cm) to Stage IIIA NSCLC (as per UICC/AJCC, 7th edition)
- Documented ALK-positive disease according to identified by a locally performed CE-marked ALK test, or centrally performed by the Ventana ALK (D5F3) immunohistochemistry (IHC) assay.
- Eastern Cooperative Oncology Group (ECOG) Performance Status of Grade 0 or 1
- Adequate hematologic and renal function as defined per protocol

Key Exclusion Criteria

Patients meeting any of the following criteria were excluded from the study:

- Pregnant or lactating women
- 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

Screening assessments included:

- CT scan (with oral/IV contrast unless contraindicated) of the chest and abdomen (including liver and adrenal glands).
- Magnetic resonance imaging (MRI) of the brain to rule out CNS metastasis. If MRI was not available, CT scans (with oral/IV contrast unless contraindicated) could be performed instead.
- Patients with metastatic disease were to be excluded from this study. Patients who had clinical signs, symptoms, biochemical abnormalities (including, but not limited to, ALP, LDH, etc.), or radiological imaging that could be suggestive of bone metastases at baseline, must undergo further investigation to exclude the presence of bone metastases at study entry. Additional appropriate imaging techniques included but are not limited to PET imaging and isotope bone scans.
- CT/MRI scans (with oral/IV contrast unless contraindicated) of the pelvis and neck should be included if clinically indicated.

Treatments

Patients in the experimental arm received alectinib at 600 mg orally BID taken with food for 24 months. Patients in the control arm received one of the protocol-specified platinum-based chemotherapy regimens.

Platinum-based chemotherapy was provided for 4 cycles, with each cycle lasting 21 days. Investigators could choose one of the permitted platinum-based chemotherapy regimens, which included the following:

- Cisplatin 75 mg/m 2 on Day 1 plus vinorelbine 25 mg/m 2 on Days 1 and 8

- Cisplatin 75 mg/m 2 on Day 1 plus gemcitabine 1250 mg/m 2 on Days 1 and 8
- Cisplatin 75 mg/m 2 on Day 1 plus pemetrexed 500 mg/m 2 on Day 1

In case of intolerability to a cisplatin-based regimen, carboplatin could be administered instead of cisplatin in one of the above combinations.

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 occured 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. After disease recurrence, patients were treated at the discretion of the investigator according to local clinical practice. No crossover in the adjuvant setting was allowed between the two arms.

Objectives

Table 3: Study objectives and endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of alectinib compared with platinum-based chemotherapy in patients with completely resected Stage Ib (tumors ≥4 cm) to Stage IIIa, ALK-positive NSCLC	• Disease-free survival (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 Objective	**Corresponding Endpoint**
• To evaluate the efficacy of alectinib compared with platinum-based chemotherapy in patients with completely resected Stage Ib (tumors ≥4 cm) to Stage IIIa, ALK-positive NSCLC	• Overall survival (OS), defined as the time from randomization to death from any cause

Outcomes/endpoints

By protocol, disease assessments were to be made every 12 weeks for the first 2 years, every 24 weeks during Years 3 to 5 and annually thereafter until recurrence.

Table 4: Objectives and estimands

Primary Efficacy Objective	Estimand Definition

• To evaluate the efficacy of alectinib compared with platinum-based chemotherapy in patients with completely resected Stage Ib (tumors ≥ 4 cm) to Stage IIIa, ALK-positive NSCLC	• Population: patients with completely resected Stage II–IIIa ALK-positive NSCLC (Stage II-IIIa population)
	• Variable: Time from randomization to the first occurrence of a DFS event (as defined in Table 1)
	• Treatments:
	  ○ Experimental: alectinib 600 mg orally BID taken with food for 24 months
	  ○ Control: protocol-specified platinum-based chemotherapy regimens for 4 cycles, with each cycle lasting 21 days. In case of intolerability to a cisplatin-based regimen, carboplatin can be administered instead of cisplatin in one of the below combinations.
	  ○ Cisplatin 75 mg/m^2 on Day 1 plus vinorelbine 25 mg/m^2 on Days 1 and 8
	  ○ Cisplatin 75 mg/m^2 on Day 1 plus gemcitabine 1250 mg/m^2 on Days 1 and 8
	  ○ Cisplatin 75 mg/m^2 on Day 1 plus pemetrexed 500 mg/m^2 on Day 1
	• Intercurrent events:
	  ○ Start of non-protocol adjuvant anti-cancer therapy prior to a DFS event
	  ○ Early discontinuation from study treatment for any reason prior to a DFS event
	• Handling of intercurrent events: A treatment policy with regards to the intercurrent events listed above will be applied for the primary analysis
	• Summary measure: Hazard ratio for DFS
	If alectinib significantly prolongs DFS in the Stage II–IIIa subpopulation, then DFS will be tested in the ITT population. The corresponding estimand is defined similarly as above but with the population as defined below:
	• Population: patients with completely resected Stage Ib (tumors ≥ 4 cm) to Stage IIIa ALK-positive NSCLC (ITT population)

Secondary Efficacy Objective	Estimand Definition

• To evaluate the efficacy of alectinib compared with platinum-based chemotherapy in patients with completely resected Stage Ib (tumors ≥ 4 cm) to Stage IIIa, ALK-positive NSCLC	• Population: patients with completely resected Stage II–IIIa ALK-positive NSCLC (Stage II-IIIa population)
	• Variable: Time from randomization to death from any cause
	• Treatments:
	  ○ Experimental: alectinib 600 mg orally BID taken with food for 24 months
	  ○ Control: protocol-specified platinum-based chemotherapy regimens for 4 cycles, with each cycle lasting 21 days. In case of intolerability to a cisplatin-based regimen, carboplatin can be administered instead of cisplatin in one of the below combinations.
	  ○ Cisplatin 75 mg/m^2 on Day 1 plus vinorelbine 25 mg/m^2 on Days 1 and 8
	  ○ Cisplatin 75 mg/m^2 on Day 1 plus gemcitabine 1250 mg/m^2 on Days 1 and 8
	  ○ Cisplatin 75 mg/m^2 on Day 1 plus pemetrexed 500 mg/m^2 on Day 1
	• Intercurrent events:
	  ○ Start of non-protocol adjuvant anti-cancer therapy
	  ○ Early discontinuation from study treatment for any reason
	• Handling of intercurrent events: A treatment policy with regards to the intercurrent events listed above will be applied for the analysis
	• Summary measure: Hazard ratio for OS
	
	OS will also be analyzed in the ITT population. As a consequence, an alternative estimand for OS is defined similarly as above but with the population as defined below:
	• Population: patients with completely resected Stage Ib (tumors ≥ 4 cm) to Stage IIIa ALK-positive NSCLC (ITT population)

In addition to the protocol-specified objectives and endpoints, the exploratory endpoint of time to central nervous system (CNS) recurrence or death was included in the SAP v2. 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 occurred first. Patients who were not reported as experiencing disease recurrence in the CNS or death were to be censored at the date of the last disease assessment. Time to CNS recurrence or death was analysed in the Stage II−IIIA subpopulation and the intent-to-treat (ITT) population, and the same methodology used for DFS was applied.

Sample size

Approximately 255 patients were expected to be randomized into the study. The number of Stage Ib patients were capped at 25% to ensure that at least 75% of all randomized patients would have Stage II-IIIa disease. The resulting intent-to-treat (ITT) population of all patients randomized would then include a minimum of 191 patients in the Stage II-IIIa subpopulation.

The sample size and the number of events required to demonstrate efficacy with regard to the primary efficacy endpoint DFS at the primary analysis were based on the following assumptions: 80% power to detect a hazard ratio (HR) of 0.55, corresponding to an improvement in median DFS from 30 months to 55 months for patients receiving alectinib compared with chemotherapy in the Stage II-IIIa subpopulation and 80% power to detect an HR of 0.58 corresponding to an improvement in median DFS from 36 months to 62 months in the ITT population.

Overall two-sided significance level of 0.05 were used with one interim analysis for DFS when approximately 67% of the total DFS events had occurred, with use of the Lan-DeMets approximation to the O'Brien-Fleming boundaries.

Based on these assumptions, the primary DFS analysis were to be conducted after approximately 89 DFS events in the Stage II-IIIa subpopulation had been observed.

Randomisation

257 patients were randomly assigned in a 1:1 allocation ratio to the two treatment arms via a block-stratified randomization procedure over a planned recruitment period of approximately 3 years. To assist balance in prognostic factors, randomization was stratified by race (Asian vs. non-Asian) and disease stage (Stage Ib [tumors ≥ 4 cm] vs. Stage II vs. Stage III). Central randomization and drug allocation were performed and managed via an IxRS.

Blinding (masking)

This was an open-label study; Study site personnel and patients were unblinded to treatment assignment information during the study.

Statistical methods

The primary and secondary efficacy analyses were performed for all randomized patients (ITT population) and for the Stage II-IIIa subpopulation. The same analysis methods were applied for both the ITT population and the Stage II-IIIa subpopulation. Patients were analyzed in the treatment group to which they were randomized.

The primary DFS analysis were to be conducted after approximately 89 DFS events in the Stage II-IIIa subpopulation had been observed. The interim analysis was performed after 59 DFS events in the Stage II-IIIa subpopulation had been observed.

Definition of primary endpoint

The primary efficacy objective for this study was to evaluate the efficacy of alectinib compared with platinum-based chemotherapy on the basis of Disease-free survival (DFS). Disease-free survival was 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, and clinical status) or death from any cause, whichever occurred first.

Primary analysis

The treatment comparison of DFS were based on a stratified log-rank test, according to the protocol-defined stratification factors as entered in the IxRS:

- Race (Asian vs. non-Asian) for the analysis in the Stage II-IIIa subpopulation, and
- Race (Asian vs. non-Asian) and disease stage (Stage Ib [tumors ≥ 4 cm] vs. Stage II vs. Stage IIIa) for the analysis in the ITT population.

Cox proportional hazards model, stratified by the protocol-defined stratification factors as entered in IxRS, as shown above, were used to estimate the HR between the two treatment arms and its 95% confidence interval (CI).

Kaplan-Meier methodology was used to estimate the median DFS for each treatment arm, and the Kaplan-Meier curves were constructed to provide a visual description of the difference between the treatment and control arms. Brookmeyer-Crowley methodology was used to construct the 95% CI for the median DFS for each treatment arm.

Missing data/Censoring

Patients who were not reported as experiencing disease recurrence, a new primary NSCLC, or death were censored at the date of the last disease assessment. If no post-baseline data was available, patients were censored at the date of randomization.

Sensitivity analyses

To assess the impact of stratification, results from an unstratified log-rank test and the unstratified HR were also be provided.

The analysis of DFS were also to be repeated by using the stratification factors as entered in the electronic Case Report Form (eCRF).

In addition, the impact of loss to follow-up on DFS were to be assessed depending on the number of patients who were lost to follow-up. If more than 5% of patients were lost to follow-up for DFS in either treatment arm, a sensitivity analysis ("worst-case" analysis) was to be performed in which patients who were lost to follow-up were to be considered to have recurrent disease at the date of the last disease assessment.

The impact of missing scheduled tumor assessments on DFS was assessed by performing a sensitivity analysis based on the interval censoring analysis methods.

An analysis of DFS on the basis of IRF assessments could be performed after centralized, independent review of response endpoints by the IRF using the same analyses as specified for DFS on the basis of investigator assessment.

The generalizability of DFS results when comparing alectinib to chemotherapy was investigated by estimating the treatment effect in subgroups based on key baseline demographics (e.g., age, sex, and race/ethnicity) and disease characteristic (e.g., disease stage, smoking history, and ECOG Performance Status). Summaries of DFS by these subgroups were provided in forest plots including unstratified HRs estimated from Cox proportional hazards models and Kaplan-Meier estimates of the median provided separately for each level of the subgroups.

Secondary and exploratory Efficacy Endpoints

Overall survival was defined as the time from the date of randomization to death due to any cause. Data for patients who were not reported as having died at the date of analysis were censored at the date when they were last known to be alive. If no post-baseline data were available, OS was censored at the date of randomization plus 1 day. The methodology used for DFS analysis was also applied for OS.

Overall survival was planned to be analyzed at the time of the DFS analyses and at the time of the final survival follow-up analysis, which will be conducted at approximately 5 years after the last patient is enrolled.

Analyses at landmark timepoints of 3, 4, and 5 years within the Stage II-IIIa subpopulation and the ITT population were performed for DFS. Rates were estimated using Kaplan-Meier methodology for each treatment arm, with 95% CIs calculated using Greenwood's formula.

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 occurred first. Patients who were not reported as experiencing disease recurrence in the CNS or death were censored at the date of the last disease assessment. Of note, data for patients who experienced non-CNS recurrence prior to an eventual CNS recurrence were censored at the date of non-CNS recurrence in this analysis.

Multiplicity

A testing hierarchy was used to control the overall type I error rate at 5% with regards to DFS in the Stage II-IIIA subpopulation and ITT population.

Disease-free survival (DFS) in the Stage II-IIIa subpopulation was first to be tested at an overall 2-sided α-level of 0.05. If this test was significant, then DFS in the ITT population was to be tested at an overall 2-sided α-level of 0.05.

The actual α-level for each test at final analysis was to be 0.0464 (in order to adjust for 1 interim analysis for efficacy).

Interim analysis

A pre-planned interim analysis was to be conducted after approximately 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 are:

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

DFS in the Stage II−IIIA subpopulation was first tested at an overall two-sided α level of 0.0118. Since a significant effect was observed in the Stage II-IIIA subpopulation, DFS in the ITT population was then tested. Since the boundaries were crossed at the pre-specified interim analysis, no further hypothesis testing will be performed at later CCODs. This interim analysis becomes the primary analysis.

Positive efficacy results at the interim analysis were not to change the conduct of the study and timing of disease assessments.

Results

Participant flow

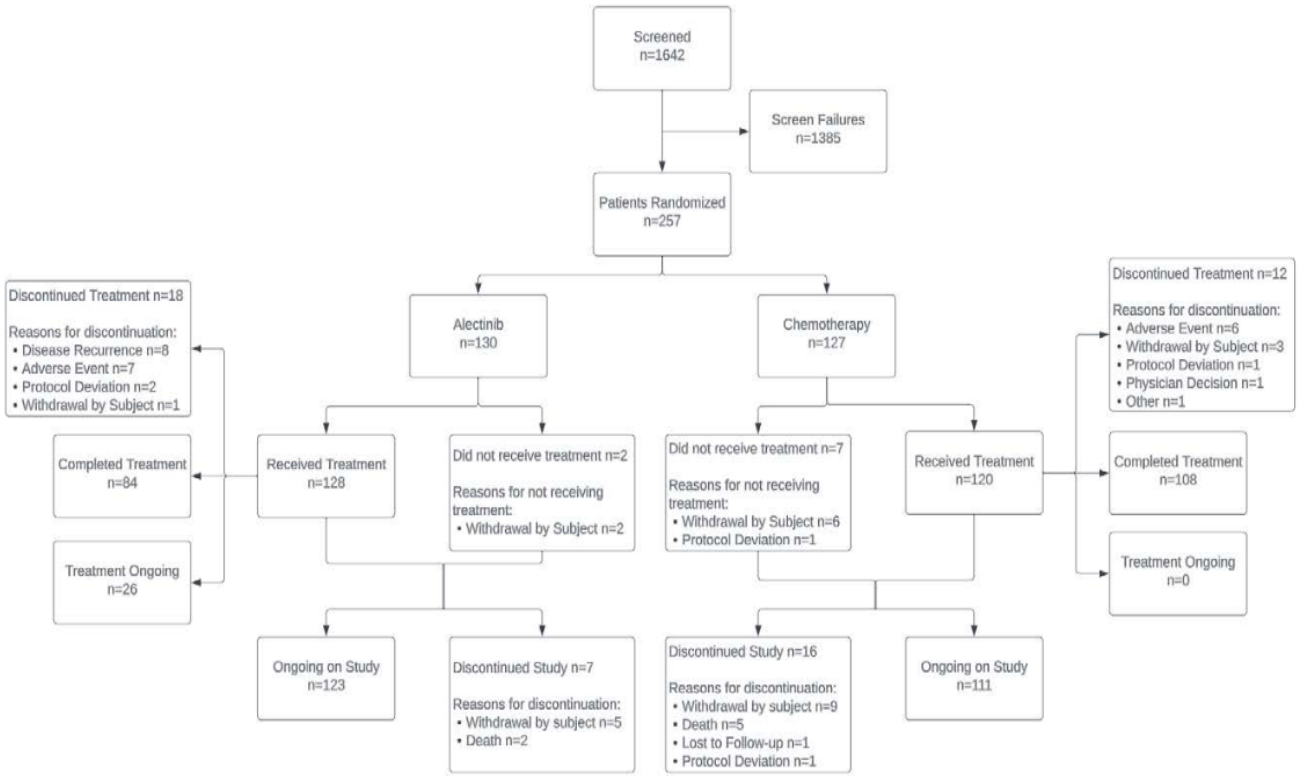


Figure 11: Participant flow

Recruitment

In total, 1642 patients were screened for inclusion in this study and 1385 patients failed screening based on information collected on the IxRS. The most common reason for screen failure was that the patient's tumour tissue sample was ALK-negative (79.5%), followed by the patient not having met inclusion criteria (14.5%).

A total of 257 patients were randomized in the study in 113 sites across 26 countries: 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), France 6 patients (4), Germany 6 patients (4), Taiwan 6 patients (5), Austria 5 patients (1), Belarus 5 patients (3), Thailand 5 patients (2), U.S. 3 patients (3), Denmark 2 patients (1), U.K. 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).

Biomarker

Of the 257 patients in the ITT population, most patients (78.5% [102 patients] in the alectinib arm and 74.8% [95 patients] in the chemotherapy arm) were tested to have ALK-positive tumors by a locally performed ALK test for enrollment. The most common local ALK testing method was the Ventana ALK IHC assay (alectinib arm: 74.5% vs. chemotherapy arm: 84.2%), followed by the Abbott

FISH test (alectinib arm: 20.6% vs. chemotherapy arm: 13.7%). Among patients who had both local and central ALK testing (96 patients in the alectinib arm vs. 86 patients in the chemotherapy arm), concordance between local and central positive results was above 90% in both arms.

Study dates

The first patient was randomized on 16 August 2018 and the last patient was randomized on 8 December 2021. The clinical cutoff date was 26 June 2023. The minimum follow-up would then be about 18.5 months, the maximum 58 months.

Conduct of the study

Table 5: 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%)

Analyses of primary and secondary efficacy analyses, as proposed in protocol versions:

Protocol version 1 05-Feb-2018	1) DFS in the Stage II-IIIA subpopulation will be tested first. An interim analysis will be conducted after approximately 67% (n=59) of DFS events for the Stage II-IIIA subpopulation (HR ≤ 0.52; p ≤ 0.0118). 2) The primary DFS analysis will be conducted after approximately 89 DFS events in the Stage II-IIIA subpopulation (two-sided p-value less than 0.0464).

	3) In the ITT population, the stopping boundary for early rejection of the null hypothesis for an overall two-sided 5% significance level is HR ≤ 0.55 (p ≤ 0.0121). If less than 67% of DFS events in the ITT population have been observed at the time of reaching the required events for the interim analysis in the Stage II-IIIA subpopulation, the stopping boundaries will be adjusted depending on the actual number of DFS events observed in the ITT population. However, the ITT interim analysis would only take place in the case of early rejection of the null hypothesis in the Stage II-IIIA subpopulation. 4) DFS analysis in the ITT population will be tested at 0.0463 at the primary analysis. <u>Optional interim analysis</u> The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis, will be documented in the Statistical Analysis Plan (SAP), and the SAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis.
Protocol versions ≥ 2 10-Apr-2018	No changes to analyses of primary or secondary efficacy analyses in protocol version 2 or thereafter (3: 23-Apr-2018, 4: 08-Nov-2019, 5: 26-Nov-2019, 6: 10-Mar-2021, 7: 16-Dec-2021).

Treatment disposition

Of 257 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 consent [6 patients] and a protocol deviation [1 patient]).

At the CCOD of 26 June 2023, on which the interim DFS analysis was based, 74.7% had completed treatment and 8.9% had discontinued from study.

Table 6: Patient treatment disposition, safety evaluable patients (DCO 26Jun2023)

	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%)

The most common chemotherapy regimen was platinum/pemetrexed (80%; 96 patients), of whom 91.7% (88 patients) completed 4 cycles, followed by platinum/vinorelbine (19.1%, 23 patients), of whom 82.6% (19 patients) completed 4 cycles. One patient received cisplatin/gemcitabine and completed 4 cycles.

Carboplatin could be substituted for cisplatin, when cisplatin was not tolerated by patients. In the chemotherapy arm, 11.7% (14 of 120 patients) were exposed to carboplatin either with pemetrexed (12 patients) or vinorelbine (2 patients).

Baseline data

Demographic and baseline characteristics

Table 7: Demographics and baseline 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%)
Age group 2 (yr)			
n	130	127	257
18-40	25 (19.2%)	13 (10.2%)	38 (14.8%)
41-60	64 (49.2%)	62 (48.8%)	126 (49.0%)
>60	41 (31.5%)	52 (40.9%)	93 (36.2%)
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%)
Weight (kg) at baseline			
n	130	127	257
Mean (SD)	68.33 (16.05)	70.96 (16.30)	69.63 (16.20)
Median	65.25	70.00	67.50
Min - Max	40.5 - 120.0	40.5 - 118.0	40.5 - 120.0
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%)
Female fertility status			
n	75	59	134
Childbearing Potential	31 (41.3%)	18 (30.5%)	49 (36.6%)
Surgically Sterile	3 (4.0%)	5 (8.5%)	8 (6.0%)
Post-Menopausal	41 (54.7%)	36 (61.0%)	77 (57.5%)

Baseline disease characteristics

Table 8: Baseline disease characteristics

	Alectinib (N=130)	Chemotherapy (N=127)	All Patients (N=257)
Time from initial diagnosis to randomization (months)			
n	129	123	252
Mean (SD)	2.21 (0.93)	2.18 (1.28)	2.19 (1.11)
Median	2.04	1.94	1.99
Min - Max	0.6 - 7.0	0.4 - 13.1	0.4 - 13.1
Site of primary tumor			
n	130	127	257
LEFT	59 (45.4%)	56 (44.1%)	115 (44.7%)
RIGHT	71 (54.6%)	71 (55.9%)	142 (55.3%)
Largest tumor diameter (cm)			
n	129	127	256
Mean (SD)	3.25 (2.24)	3.08 (1.70)	3.17 (1.99)
Median	3.00	2.70	2.80
Min - Max	0.8 - 17.0	0.6 - 10.0	0.6 - 17.0
Histology			
n	130	127	257
Squamous	6 (4.6%)	3 (2.4%)	9 (3.5%)
Non-Squamous	124 (95.4%)	124 (97.6%)	248 (96.5%)
Subtype histology in non-squamous			
n	124	124	248
Adenocarcinoma	119 (96.0%)	119 (96.0%)	238 (96.0%)
Mixed (Not Including Small Cell)	2 (1.6%)	0	2 (0.8%)
NSCLC/NOS	2 (1.6%)	1 (0.8%)	3 (1.2%)
Other	1 (0.8%)	4 (3.2%)	5 (2.0%)
Primary tumor stage per AJCC 7th edition			
n	130	127	257
T1a	30 (23.1%)	37 (29.1%)	67 (26.1%)
T1b	21 (16.2%)	22 (17.3%)	43 (16.7%)
T2a	59 (45.4%)	47 (37.0%)	106 (41.2%)
T2b	4 (3.1%)	10 (7.9%)	14 (5.4%)
T3	15 (11.5%)	8 (6.3%)	23 (8.9%)
T4	1 (0.8%)	3 (2.4%)	4 (1.6%)
Regional lymph node stage			
n	130	127	257
N0	21 (16.2%)	18 (14.2%)	39 (15.2%)
N1	45 (34.6%)	43 (33.9%)	88 (34.2%)
N2	64 (49.2%)	66 (52.0%)	130 (50.6%)
Distant metastasis stage			
n	130	127	257
M0	130 (100%)	127 (100%)	257 (100%)
Initial diagnosis staging per AJCC 7th edition (eCRF)			
n	130	127	257
Stage IB	17 (13.1%)	9 (7.1%)	26 (10.1%)
Stage IIA	38 (29.2%)	42 (33.1%)	80 (31.1%)
Stage IIB	5 (3.8%)	5 (3.9%)	10 (3.9%)
Stage IIIA	70 (53.8%)	71 (55.9%)	141 (54.9%)
Initial diagnosis staging per AJCC 7th edition (IxRS)			
n	130	127	257
Stage IB	14 (10.8%)	12 (9.4%)	26 (10.1%)
Stage II	47 (36.2%)	45 (35.4%)	92 (35.8%)
Stage IIIA	69 (53.1%)	70 (55.1%)	139 (54.1%)

Subsequent therapy

Table 9: Subsequent anticancer systemic therapy by preferred name , ITT patients (DCO 26Jun2023)

Other Treatment	Alectinib (N=130)	Chemotherapy (N=127)	All Patients (N=257)
Total number of patients with at least one treatment	16 (12.3%)	39 (30.7%)	55 (21.4%)
Total number of treatments	27	48	75
ALECTINIB	5 (3.8%)	25 (19.7%)	30 (11.7%)
BRIGATINIB	4 (3.1%)	4 (3.1%)	8 (3.1%)
CISPLATIN	4 (3.1%)	2 (1.6%)	6 (2.3%)
CARBOPLATIN	4 (3.1%)	1 (0.8%)	5 (1.9%)
ALECTINIB HYDROCHLORIDE	0	4 (3.1%)	4 (1.6%)
CRIZOTINIB	0	4 (3.1%)	4 (1.6%)
PEMETREXED	3 (2.3%)	1 (0.8%)	4 (1.6%)
VINORELBINE TARTRATE	3 (2.3%)	0	3 (1.2%)
DURVALUMAB	1 (0.8%)	1 (0.8%)	2 (0.8%)
LORLATINIB	0	2 (1.6%)	2 (0.8%)
PACLITAXEL	1 (0.8%)	1 (0.8%)	2 (0.8%)
AFATINIB	1 (0.8%)	0	1 (0.4%)
CERITINIB	0	1 (0.8%)	1 (0.4%)
GIMERACIL;OTERACIL POTASSIUM;TEGAFUR	1 (0.8%)	0	1 (0.4%)
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	0	1 (0.8%)	1 (0.4%)
VINORELBINE	0	1 (0.8%)	1 (0.4%)

Numbers analysed

Table 10: Analysis Populations, Intent-to-Treat Patients

	Alectinib (N=130)	Chemotherapy (N=127)	All Patients (N=257)
Intent-to-treat Patients	130	127	257
Intent-to-Treat Stage II-IIIA (IxRS) Patients	116	115	231
Safety-Evaluable Patients (Treatment Received)	128	120	248
PK-Evaluable Patients	124	0	124

Patients are counted by treatment assigned unless stated otherwise.

Outcomes and estimation

At the CCOD of 26 June 2023, 59 DFS events had occurred in the Stage II-IIIA subpopulation and 65 DFS events in the ITT population. The pre-specified DFS interim analysis was conducted by iDMC and the stopping boundaries for both populations were crossed.

The median duration of survival follow-up was 27.8 months in the alectinib arm and 28.4 months in the chemotherapy arm.

Primary endpoint: DFS in Stage II-IIIA

Table 11: DFS in Stage II-IIIA

	Alectinib	Chemotherapy
Primary Efficacy Endpoint		
	N = 116	N = 115
Patients with event (%)	14 (12.1%)	45 (39.1%)
Median DFS (95% CI), months	NE (NE, NE)	44.4 (27.8, NE)
Stratified HR (95% CI)	0.24 (0.13, 0.45)	
p-value (stratified log-rank)	< 0.0001	
24 Month event free rate (%) (95% CI)	93.8 (89.36, 98.25)	63.0 (53.33, 72.68)
Patients remaining at risk	67	48
36 Month event free rate (%) (95% CI)	88.3 (80.83, 95.83)	53.3 (42.34, 64.16)
Patients remaining at risk	35	23

DFS = disease-free survival; HR = hazard ratio; ITT = intent-to-treat; NE = not estimable.

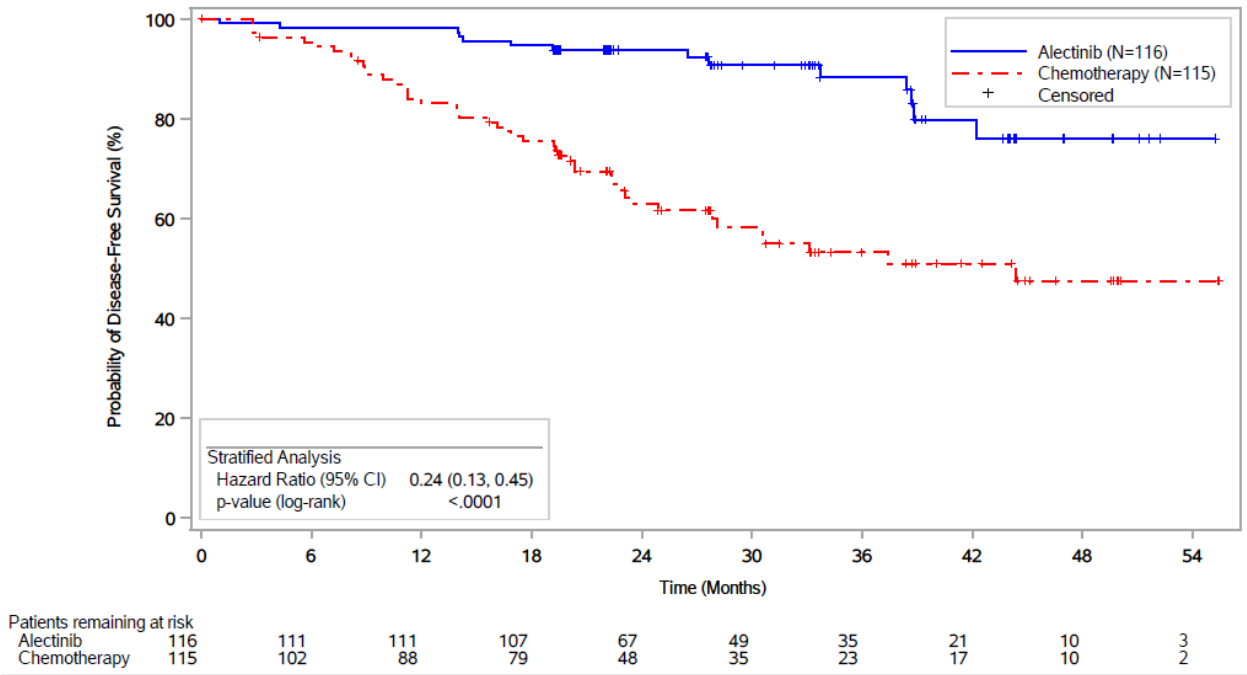


Figure 12: Kaplan-Meier Plot of disease-free survival, stage II-IIIA patients (DCO 26 Jun 2023)

Primary endpoint: DFS in the Stage IB (tumour ≥ 4 cm)-IIIA (ITT)

Table 12: DFS in the Stage IB (tumour ≥ 4 cm)-IIIA (ITT)

	Alectinib	Chemotherapy
DFS in ITT (Stage IB-IIIA)	N = 130	N = 127
Patients with event (%)	15 (11.5%)	50 (39.4%)
Median DFS (95% CI), months	NE (NE, NE)	41.3 (28.5, NE)
Stratified HR (95% CI)	0.24 (0.13, 0.43)	
p-value (stratified log-rank)	< 0.0001	
24 Month event free rate (%) (95% CI)	93.6 (89.38, 97.91)	63.7 (54.59, 72.90)
Patients remaining at risk	74	55
36 Month event free rate (%) (95% CI)	88.7 (81.76, 95.63)	54.0 (43.73, 64.21)
Patients remaining at risk	39	27

DFS = disease-free survival; HR = hazard ratio; ITT = intent-to-treat; NE = not estimable.

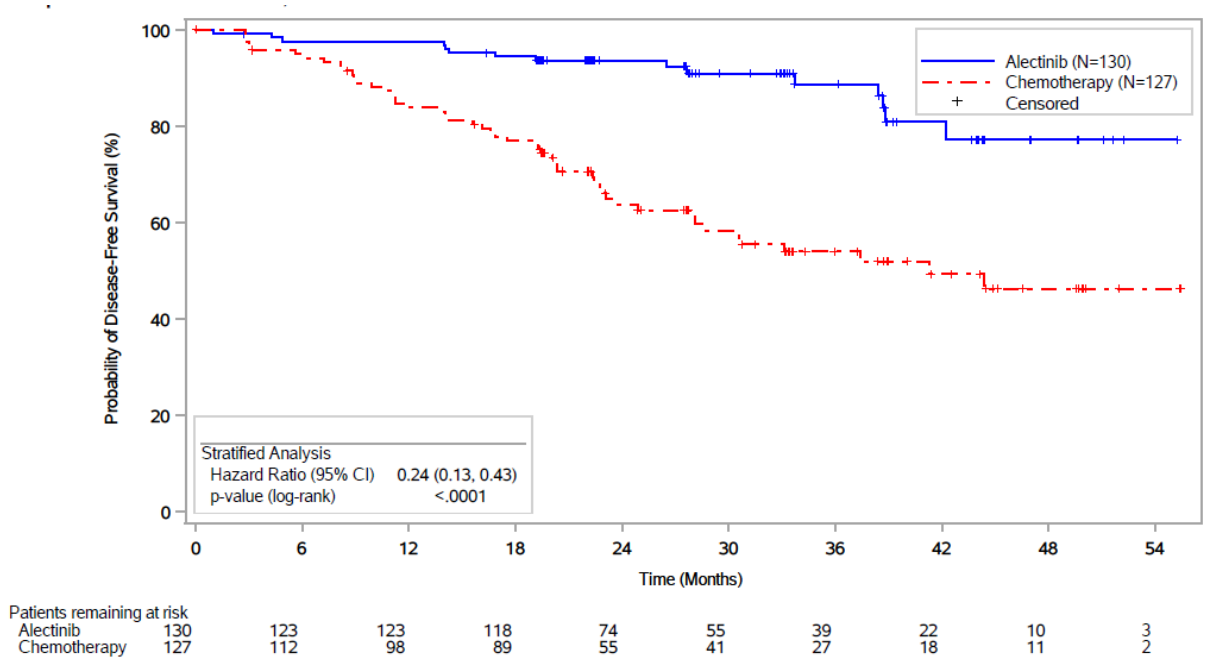


Figure 13: Kaplan-Meier Plot of disease-free survival, stage IB-IIIA patients , ITT population (DCO 26 Jun 2023)

Reasons for censoring of DFS events

Table 13: DFS Events and descriptions, Stage II-IIIA Patients

Event	Event Description	Alectinib (N=116)	Chemotherapy (N=115)
Censored	Last Tumor Assessment	99 (85.3%)	63 (54.8%)
Censored	Randomization	3 (2.6%)	7 (6.1%)
DFS Event	Death	0	1 (0.9%)
DFS Event	Disease Recurrence	14 (12.1%)	44 (38.3%)

DFS = Disease-free survival

Table 14: DFS Events and descriptions, Intent-to-treat Patients

Event	Event Description	Alectinib (N=130)	Chemotherapy (N=127)
Censored	Last Tumor Assessment	112 (86.2%)	69 (54.3%)
Censored	Randomization	3 (2.3%)	8 (6.3%)
DFS Event	Death	0	1 (0.8%)
DFS Event	Disease Recurrence	15 (11.5)	49 (38.6%)

DFS = Disease-free survival

The patients had a window to provide the assessments of 7 days within the first 2 years and 14 days during years 3-5 after randomization. As such, 27 March 2023 was considered for patients randomized on or after 26 June 2021 (instead of 03 April 2023) and 26 December 2022 for all other patients (instead of 09 January 2023), as the dates of the administrative censoring window.

Table 15: Non-administrative censoring reasons, non-administrative censored patients

	Alectinib (N=11)	Chemotherapy (N=13)	All Patients (N=24)
Non-Administrative Censoring Reasons			
Lost to follow-up	0	1 (7.7%)	1 (4.2%)
No Assessment Done Within The Window	6 (54.5%)	3 (23.1%)	9 (37.5%)
Protocol Deviation	0	1 (7.7%)	1 (4.2%)
Withdrawal by subject	5 (45.5%)	8 (61.5%)	13 (54.2%)

Administrative censoring was defined as -13 weeks for patients randomized 2 years before the CCOD and -26 weeks for all other patients.
Reasons for study discontinuation were selected for patients censored outside the administrative window.
Some patients may have missing disease assessments or discontinued from the disease assessment period.

In the ITT population, 24 of 257 patients were censored outside the administrative censoring window, with no concerning pattern across arms. The loss of information and potential for impact on the primary endpoint is considered limited.

Table 16: Sensitivity Analyses on DFS in the Stage II-IIIA Population

	Alectinib (N = 116)	Chemotherapy (N = 115)
Primary analysis		
Patients with event (%)	14 (12.1%)	45 (39.1)
Median DFS (95% CI), months	NE (NE, NE)	44.4 (27.8, NE)
Stratified HR (95% CI); p-value	0.24 (0.13, 0.45); p < 0.0001	
Missing disease assessments[a]		
Patients with event (%)	14 (12.1%)	45 (39.1%)
Median DFS (95% CI), months	NE (NE, NE)	44.4 (27.8, NE)
Stratified HR (95% CI); p-value	0.24 (0.13, 0.43); p < 0.0001	
Stratification errors[b]		
Patients with event (%)	14 (12.4%)	47 (39.8%)
Median DFS (95% CI), months	NE (NE, NE)	37.4 (27.8, NE)
Stratified HR (95% CI); p-value	0.24 (0.13, 0.44); p < 0.0001	
Ukraine–Russia conflict[c]		
Patients with event (%)	14 (12.1%)	43 (37.4%)
Median DFS (95% CI), months	NE (NE, NE)	44.4 (27.8, NE)
Stratified HR (95% CI); p-value	0.25 (0.14, 0.46); p < 0.0001	

DFS = disease-free survival; HR = hazard ratio; NE = not estimable.
a: The impact of missing scheduled tumor assessments on DFS was assessed by performing a sensitivity analysis based on the interval censoring analysis methods.
b: DFS analysis was repeated by using the stratification factors as entered in the electronic Case Report Form (eCRF).
c: Due to the potential inability to conduct site inspections or source data verification in Russia and/or Ukraine, a sensitivity analysis was performed on DFS by censoring data from sites in Russia and/or Ukraine at the onset of the crisis, which was 24 February 2022.

The Applicant provided results from a BICR assessment, reported in "Study BO40336 (ALINA) Retrospective Blinded Independent Central Review of Disease-Free Survival Data, November 2023", during pocedure. The BICR analysis performed for the ITT population was consistent with the INV-DFS results (stratified HR = 0.30 [95% CI: 0.17, 0.54]), as was the analysis for the Stage II-IIIA Population, with stratified HR 0.29 (95% CI: 0.15, 0.55).

Secondary endpoint:

Overall survival

Table 17: Overall Survival, Intent-to-treat patients

	Alectinib (N=130)		Chemotherapy (N=127)
Patients with event (%)	2 (1.5%)		4 (3.1%)
Earliest contributing event			
Death	2		4
Patients without event (%)	128 (98.5%)		123 (96.9%)
Time to event (months)			
Median	NE		NE
95% CI	NE		NE
25% and 75%-ile	NE		NE
Range	0* - 55*		0* - 55*
Stratified Analysis			
p-value (log-rank)		0.3603	
Hazard Ratio		0.46	
95% CI		(0.08, 2.52)	
Unstratified Analysis			
p-value (log-rank)		0.3663	
Hazard Ratio		0.47	
95% CI		(0.09, 2.54)	

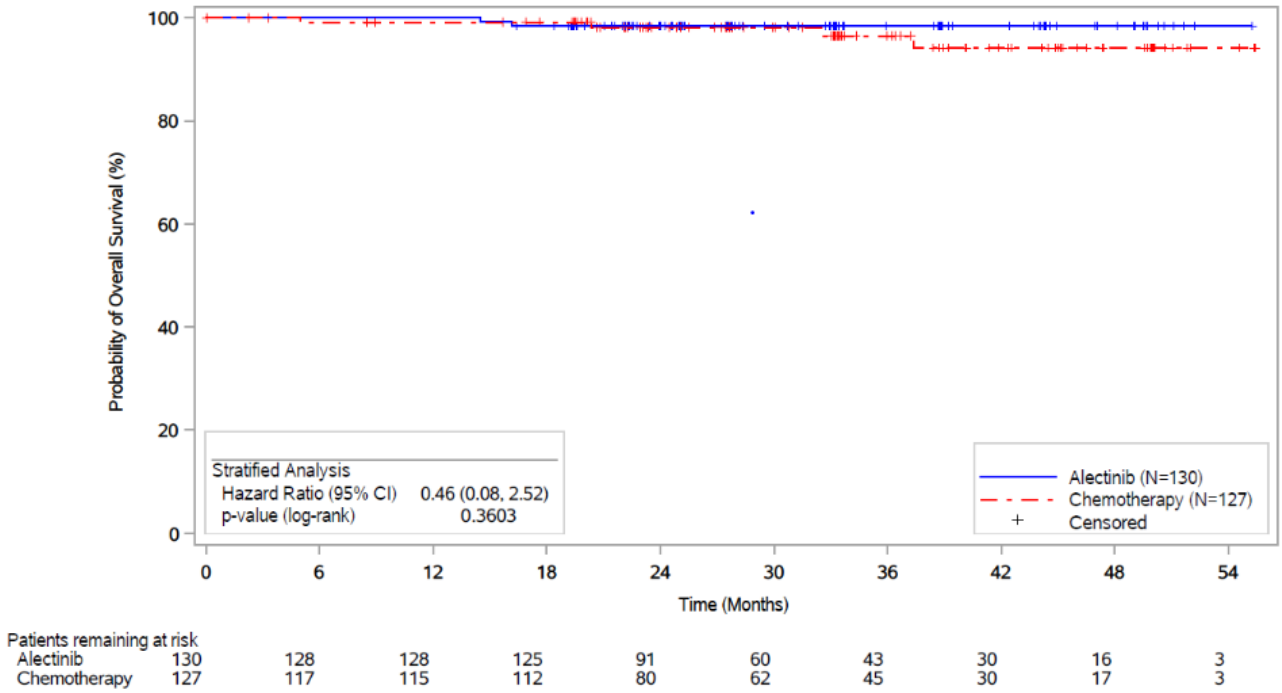


Figure 14: Kaplan-Meier Plot of overall survival, intent-to-treat Patients

Exploratory endpoint: CNS effects

Table 18: Time to CNS Recurrence or Death in ITT (Stage IB-IIIA)

	N = 130	N = 127
Patients with event (%)	5 (3.8%)	18 (14.2%)
Median time to CNS recurrence (95% CI), months	NE (NE, NE)	NE (NE, NE)
Stratified HR (95% CI)	0.22 (0.08, 0.58)	
24 Month event free rate (%) (95% CI)	98.4 (96.11, 100.00)	85.8 (78.83, 92.82)
Patients remaining at risk	74	57
36 Month event free rate (%) (95% CI)	95.5 (90.99, 99.99)	79.7 (70.44, 89.03)
Patients remaining at risk	39	27

ITT = intent-to-treat; NE = not estimable; CNS-DFS = time to CNS recurrence or death.

	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event	15 (11.5%)	49 (38.6%)
Local recurrence of Lung Cancer	8 (6.2%)	20 (15.7%)
Regional recurrence of Lung Cancer	5 (3.8%)	12 (9.4%)
Distant recurrence of Lung Cancer	5 (3.8%)	27 (21.3%)
New Primary Lung Cancer	1 (0.8%)	0
Sites of Distant recurrence		
Adrenal gland	0	3 (2.4%)
Bone	1 (0.8%)	8 (6.3%)
Brain	4 (3.1%)	14 (11.0%)
Kidney	0	1 (0.8%)
Lymph Node	0	2 (1.6%)
Other	1 (0.8%)	0
Peritoneum	0	1 (0.8%)
Site of New Primary Lung Cancer		
Not Applicable	1 (0.8%)	0

Figure 15: Location of first documented recurrence or new primary NSCLC, Intent-to-treat patients

Ancillary analyses

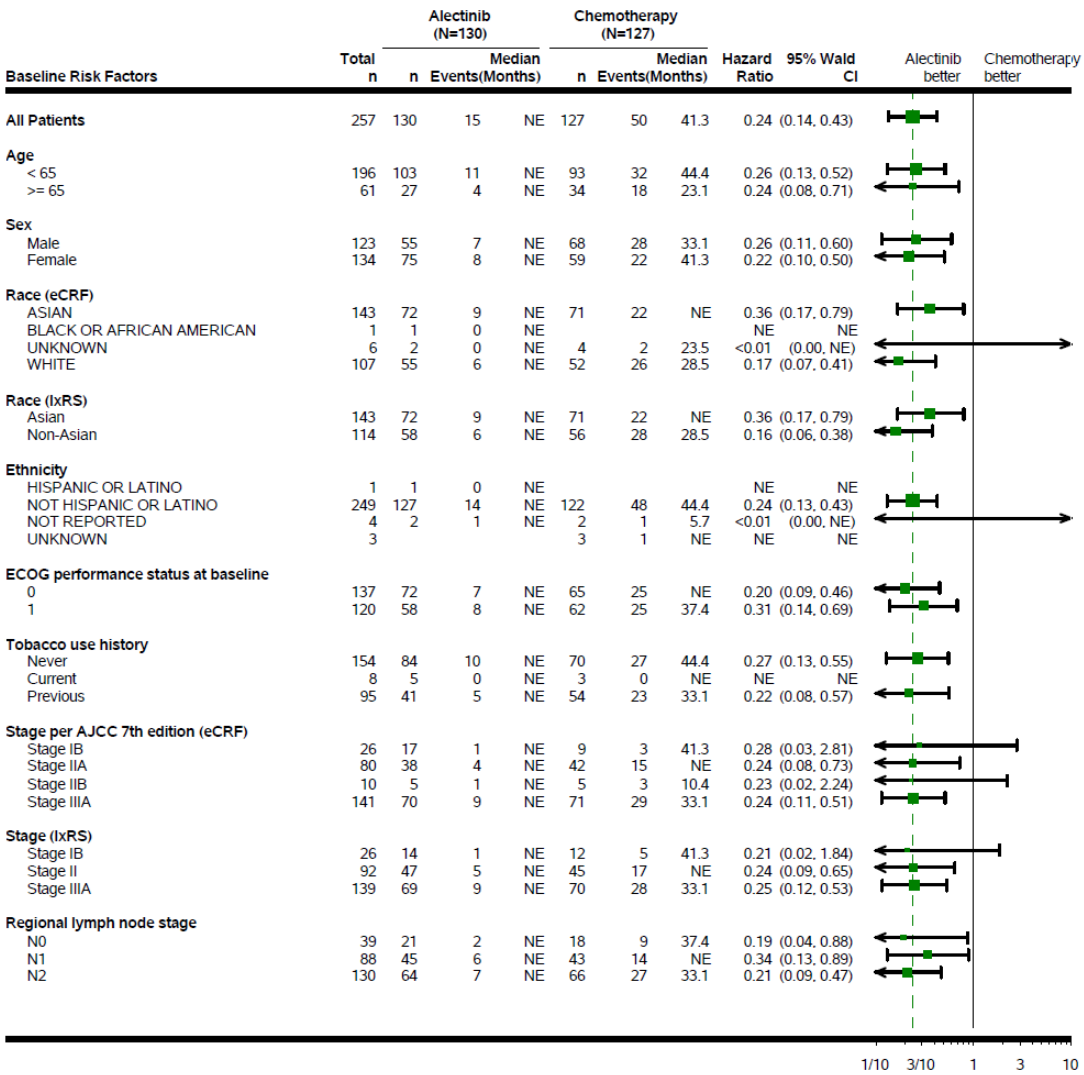


Figure 16: Forest plot for subgroup analysis of disease free survival, intent to treat patients

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 19: Summary of Efficacy for trial BO40336 (ALINA)

Title: Study BO40336, (ALINA 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)		
Study identifier	Protocol Number: BO40336, EudraCT number: 2017-004331-37, ClinicalTrials.gov Identifier: NCT03456076	
Design	Study BO40336 (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, (negative margins), histologically-confirmed, Stage IB (tumors ≥4 cm)-Stage IIIA NSCLC, as per UICC/AJCC 7th edition, with documented ALK positive disease, who met all required eligibility criteria. Eligible patients were randomized in a 1:1 fashion to treatment with alectinib or platinum-based chemotherapy. The primary endpoint of the study is disease-free survival (DFS) as assessed by the investigator, while overall survival (OS) is a secondary endpoint. One interim analysis for efficacy was planned for DFS, to be conducted after approximately 67% of events were observed in the Stage II-IIIA subpopulation (i.e., approximately 59 DFS events). The Sponsor remained blinded to the treatment assignment information until the boundary was crossed for statistical significance of the planned DFS interim analysis which was reviewed by the independent Data Monitoring Committee (iDMC).	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	First patient enrolled: 16-August-2018. Data cut-off (Efficacy and safety): 26-June-2023, (PK): 28-February-2023 not applicable not applicable
Hypothesis	Superiority. The ALINA study was designed to demonstrate superiority of alectinib compared with chemotherapy with 80% power to detect a target hazard ratio (HR) of 0.55 in the Stage II-IIIA subpopulation, and HR of 0.58 in the ITT population (Stage IB-IIIA) in the primary analysis of DFS per investigator. A testing hierarchy was used to control the overall type I error rate at 5% with regards to DFS in the Stage II-IIIA subpopulation and ITT population.	
Treatments groups	Alectinib	Alectinib 600 mg (four 150 mg capsules) was administered orally BID with food in the morning and evening. Alectinib was administered until the completion of the treatment period (24 months); recurrence of disease; unacceptable toxicity; withdrawal of consent; or death; whichever occurred first. 130 patients enrolled and randomized in the alectinib arm.
	Chemotherapy	Investigators could choose one of the permitted platinum-based chemotherapy regimens, which include the following: • Cisplatin 75 mg/m2 on Day 1 plus vinorelbine 25 mg/m2 on Days 1 and 8 • Cisplatin 75 mg/m2 on Day 1 plus gemcitabine 1250 mg/m2 on Days 1 and 8 • Cisplatin 75 mg/m2 on Day 1 plus pemetrexed 500 mg/m2 on Day 1 In case of intolerability to a cisplatin-based regimen, carboplatin could be administered instead of cisplatin in one of the above combinations. Chemotherapy was administered until the completion of the treatment period (four 21-day cycles); recurrence of disease; unacceptable toxicity; withdrawal of consent; or death; whichever

			occurred first. 127 patients enrolled and randomized in the chemotherapy arm.
Endpoints and definitions	Primary endpoint	Disease-Free Survival (INV-DFS)	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 endpoint	Overall survival (OS)	OS, defined as the time from randomization to death from any cause
	Exploratory endpoint	Time to CNS recurrence or death (CNS-DFS)	Time to central nervous system (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 occurred first.
Database lock	Clinical cut-off date: 26-June-2023		
Results and Analysis			
Analysis description	Primary Analysis INV-DFS (Stage II-IIIA)		
Analysis population and time point description	All randomised patients in the Stage II-IIIA subpopulation CCOD: 26-June-2023		
Descriptive statistics and estimate variability	Treatment group	Alectinib	Chemotherapy
	Number of subject	116	115
	Patients with DFS event (%)	14 (12.1%)	45 (39.1%)
	Median DFS (95% CI), months	NE (NE, NE)	44.4 (27.8, NE)
	24 Month event free rate (%) (95% CI)	93.8 (89.36, 98.25)	63.0 (53.33, 72.68)
	Patients remaining at risk	67	48
	36 Month event free rate (%) (95% CI)	88.3 (80.83, 95.83)	53.3 (42.34, 64.16)
	Patients remaining at risk	35	23
Effect estimate per comparison	DFS	Comparison groups	Alectinib vs Chemotherapy
		Hazard ratio	0.24
		95% Confidence Interval	(0.13, 0.45)
		P-value	< 0.0001
Notes	Not applicable		
Analysis description	Primary Analysis INV-DFS (ITT)		

Analysis population and time point description	All randomised patients in the Stage IB-IIIA population (ITT) CCOD: 26-June-2023		
Descriptive statistics and estimate variability	Treatment group	Alectinib	Chemotherapy
	Number of subject	130	127
	Patients with DFS event (%)	15 (11.5%)	50 (39.4%)
	Median DFS (95% CI), months	NE (NE, NE)	41.3 (28.5, NE)
	24 Month event free rate (%) (95% CI)	93.6 (89.38, 97.91)	63.7 (54.59, 72.90)
	Patients remaining at risk	74	55
	36 Month event free rate (%) (95% CI)	88.7 (81.76, 95.63)	54.0 (43.73, 64.21)
	Patients remaining at risk	39	27
Effect estimate per comparison	DFS	Comparison groups	Alectinib vs Chemotherapy
		Hazard ratio	0.24
		95% Confidence Interval	(0.13, 0.43)
		P-value	< 0.0001
Notes	Not applicable		
Analysis description	Secondary analysis: Overall Survival in the ITT population (Pre-specified)		
	Treatment Group	Alectinib	Chemotherapy
	Number of subjects	130	127
	Median duration of survival follow-up (months)	27.8	28.4
	Patients with event (%)	2 (1.5%)	4 (3.1%)
	Median OS (95% CI), months	NE (NE, NE)	NE (NE, NE)
	Stratified HR (95% CI)	0.46 (0.08, 2.52)	
Notes	The secondary endpoint of OS was immature with low event-to-patient ratio (6 events: 2/130 deaths in the alectinib arm vs. 4/127 deaths in the chemotherapy arm) in the ITT population.		
Analysis description	Exploratory Analysis: CNS-DFS in the ITT Population (pre-specified)		
	Treatment group	Alectinib	Chemotherapy
	Number of subject	130	127
	Patients with event (%)	5 (3.8%)	18 (14.2%)
	Median time to CNS recurrence (95% CI), months	NE (NE, NE)	NE (NE, NE)

	Stratified HR (95% CI)	0.22 (0.08, 0.58)	
	24 Month event free rate (%) (95% CI)	98.4 (96.11, 100.00)	85.8 (78.83, 92.82)
	Patients remaining at risk	74	57
	36 Month event free rate (%) (95% CI)	95.5 (90.99, 99.99)	79.7 (70.44, 89.03)
	Patients remaining at risk	39	27

Clinical studies in special populations

Table 20: Demographic and Baseline Characteristics, Intent-to-Treat Patients Cut-off Date: 26JUN2023

	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%)
65-74	24 (18.5%)	31 (24.4%)	55 (21.4%)
75-84	3 (2.3%)	2 (1.6%)	5 (1.9%)
>84	0	1 (0.8%)	1 (0.4%)
Age group 2 (yr)			
n	130	127	257
18-40	25 (19.2%)	13 (10.2%)	38 (14.8%)
41-60	64 (49.2%)	62 (48.8%)	126 (49.0%)
>60	41 (31.5%)	52 (40.9%)	93 (36.2%)

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The ALINA study was 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.

The sample size calculation was based on an expected hazard ratio (HR) of 0.55 and 0.58 in the Stage II-IIIa and the ITT population respectively. The Stage IB subpopulation were to be capped at 25% of the total sample size in order to provide adequate power for the Stage II-IIIa subgroup analysis. The

actual proportion of patients in the Stage IB subgroup was around 10%. The randomization was stratified by race (Asian vs. non-Asian) and disease stage (Stage IB vs. Stage II vs. Stage III). This assessment is based on data from the interim analysis with 59 and 65 events in the Stage II-IIIa subpopulation and the ITT population respectively, with a data cut off on 26th June 2023.

Two populations were analysed in this study, a subpopulation consisting of Stage II-IIIa and the ITT population also including stage Ib, tumour size ≥4cm. The type I error was controlled hierarchically for the two populations which is accepted. The complement population (type Ib) has been presented among the forest plots of subgroup analyses. The statistical methods for primary and secondary endpoint analyses were mostly standard and straight forward. Since the interim analysis was statistically significant in its primary analysis, it becomes the primary analysis, and no further hypothesis testing will be performed at later time points. The only endpoint included in the testing hierarhy was DFS. Hence, there were no type one error control for OS or other endpoints.

Efficacy data and additional analyses

At the first interim analysis (CCOD 26 June 2023), the ALINA study met its primary endpoint, demonstrating improvement in DFS with alectinib over chemotherapy in two prespecified populations: the Stage II-IIIA subpopulation and the ITT Population (Stage IB-IIIA ALK-positive NSCLC after surgical resection). OS data were immature at the time of the CCOD.

Clinical benefit in the adjuvant setting depends on indication of a cure rate i.e., that a non-transient effect on DFS is apparent in the plateau of KM-curves. The minimum duration of follow-up, based on trial dates, was about 18.5 months, the maximum about 58 months. The median duration of survival follow-up was 27.8 months in the alectinib arm and 28.4 months in the chemotherapy arm. About 66% of patients in the alectinib arm had completed alectinib treatment, 20% were still ongoing, and 14% had discontinued for disease progression, adverse events, protocol deviation or withdrawal by subject. In view of duration of follow-up and rate of completion of therapy, obtained efficacy results are deemed sufficient for approval. However, to confirm the persistence of treatment effect of alectinib once treatment has been discontinued, the MAH has committed to submitting updated DFS analysis by Q3 2025. Furthermore due to the immaturity of the OS data at the time of the primary analysis, final OS results will also be provided by Q3 2027. These updated efficacy results will be submitted as Annex II conditions (Post-authorisation efficacy study (PAES).

With regards to the wording of indication included in section 4.1 of the SmPC, 'at high risk of recurrence' was included with a reference to section 5.1 where the selection criteria for high risk of recurrence, including tumour size (stage IB (≥ 4 cm) – IIIA were stated.

The word 'complete' before tumour resection was also added in order to better reflect the population included in the clinical trial.

Exploratory analyses indicating what the applicant considers a clinically meaningful prolongation of CNS-DFS were conducted (stratified HR = 0.22; 95% CI: 0.08, 0.58). The SAP states that data for patients who experienced non-CNS recurrence prior to an eventual CNS recurrence will be censored at the date of non-CNS recurrence in this analysis. Of note, a significant proportion of distant recurrences where CNS recurrences: 5 (3.8%) and 27 (21.3%) distant recurrences were recorded for alectinib and chemotherapy arms, respectively, with site "brain" reported in 4 (3.1%) and 14 (11%) cases. That this corresponds to a treatment effect is likely, but this analysis, added to the final SAP version, was not controlled for multiplicity.

2.4.4. Conclusions on the clinical efficacy

Based on the results of the ALINA study, the efficacy of Alecensa as monotherapy for the adjuvant treatment of NSCLC following complete resection has been shown in the studied population (stage IB, tumour size ≥4cm - IIIA). However updated descriptive DFS and updated OS data from the BO40336 study will be submitted by the MAH as a post-authorisation efficacy study (Annex II condition) in order to confirm the efficacy of Alecensa in the adjuvant setting.

2.5. Clinical safety

Introduction

The key safety data in support of this application derive from the primary analysis of study BO40336 (ALINA) in patients with ALK-positive NSCLC, with data cut-off date 26-Jun-2023.

The evaluation is based on safety data from 128 patients exposed to a starting dose of alectinib 600 mg orally, twice a day (BID). A total of 248 patients (128 patients in the alectinib arm and 120 patients in the chemotherapy arm) received at least one study treatment and were considered for the safety-evaluable population.

Pooled safety data from studies BO28984, NP28761, and NP28673 conducted in the advanced NSCLC (aNSCLC) patients receiving alectinib 600 mg BID (N=405) are included to provide a point of reference on the safety profile of alectinib as monotherapy.

Patient exposure

Table 21: Exposure to Alectinib, Safety-Evaluable Patients (ALINA)

	Alectinib (N=128)
Treatment duration (months)	
n	128
Mean (SD)	21.3 (6.3)
Median	23.9
Min - Max	0 - 25
Treatment duration (months)	
n	128
0 - <=6	11 (8.6%)
>6 - <=12	1 (0.8%)
>12- <=18	4 (3.1%)
>18 - <=24	84 (65.6%)
>24 - <=30	28 (21.9%)
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

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. Alectinib Exposure, Safety-Evaluable Patients. Protocol: BO40336. Snapshot Date: 03AUG2023, Clinical Data Cut-off Date: 26JUN2023.

Table 22: Exposure to Chemotherapy, Safety-Evaluable Patients (ALINA)

	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
1 Cycle	8 (6.7%)	2 (14.3%)	3 (2.5%)
2 Cycles	9 (7.6%)	7 (50.0%)	1 (0.8%)
3 Cycles	5 (4.2%)	4 (28.6%)	8 (6.7%)
4 Cycles	97 (81.5)	1 (7.1%)	108 (90.0%)

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.

Adverse events

Overview of adverse events

Table 23: Overview of Adverse Events, Safety-Evaluable Patients (ALINA)

	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%)

Investigator text for AEs encoded using MedDRA version 26.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in

which multiple occurrences of the same AE are counted separately. Includes AEs with onset from first dose of study drug. Protocol: BO40336 Snapshot Date: 03AUG2023, Clinical Data Cut-off Date: 26JUN2023.

Adverse events

Table 24: Adverse events with a difference in incidence rate of at least 5% in between treatment arms, safety-evaluable patients

MedDRA System Organ Class MedDRA Preferred Term	Alectinib (N=128)	Chemotherapy (N=120)
Gastrointestinal disorders		
Nausea	10 (7.8%)	87 (72.5%)
Constipation	54 (42.2%)	30 (25.0%)
Vomiting	9 (7.0%)	30 (25.0%)
Investigations		
Aspartate aminotransferase increased	53 (41.4%)	6 (5.0%)
Blood creatine phosphokinase increased	55 (43.0%)	1 (0.8%)
Alanine aminotransferase increased	43 (33.6%)	11 (9.2%)
Blood bilirubin increased	43 (33.6%)	1 (0.8%)
Blood alkaline phosphatase increased	32 (25.0%)	4 (3.3%)
Blood creatinine increased	19 (14.8%)	6 (5.0%)
White blood cell count decreased	2 (1.6%)	23 (19.2%)
Neutrophil count decreased	3 (2.3%)	21 (17.5%)
Weight increased	17 (13.3%)	1 (0.8%)
Bilirubin conjugated increased	11 (8.6%)	0
General disorders and administration site conditions		
Malaise	6 (4.7%)	16 (13.3%)
Oedema peripheral	13 (10.2%)	1 (0.8%)
Infections and infestations		
COVID-19	37 (28.9%)	1 (0.8%)
Urinary tract infection	11 (8.6%)	2 (1.7%)
Upper respiratory tract infection	9 (7.0%)	1 (0.8%)
Metabolism and nutrition disorders		
Decreased appetite	7 (5.5%)	35 (29.2%)
Hyperuricaemia	12 (9.4%)	2 (1.7%)
Blood and lymphatic system disorders		
Neutropenia	2 (1.6%)	19 (15.8%)
Leukopenia	1 (0.8%)	9 (7.5%)
Musculoskeletal and connective tissue disorders		
Myalgia	36 (28.1%)	2 (1.7%)
Arthralgia	10 (7.8%)	2 (1.7%)
Skin and subcutaneous tissue disorders		
Rash	18 (14.1%)	7 (5.8%)
Nervous system disorders		
Dysgeusia	13 (10.2%)	3 (2.5%)
Respiratory, thoracic and mediastinal disorders		
Cough	19 (14.8%)	4 (3.3%)
Dyspnoea	13 (10.2%)	3 (2.5%)
Hiccups	0	9 (7.5%)
Productive cough	7 (5.5%)	0
Injury, poisoning and procedural complications		
Product dose omission issue	21 (16.4%)	0
Product dose omission in error	16 (12.5%)	0
Cardiac disorders		
Bradycardia	10 (7.8%)	0

Investigator text for AEs encoded using MedDRA version 26.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. Includes AEs with onset from first dose of study drug. Protocol: BO40336 Snapshot Date: 03AUG2023, Clinical Data Cut-off Date: 26JUN2023.

Selected adverse events

Table 25: 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

Investigator text for AEs encoded using MedDRA version 26.0. All counts represent patients. Multiple occurrences of the same AE in one individual are counted only once.
Protocol: BO40336. Snapshot Date: 03AUG2023, Clinical Data Cut-off Date: 26JUN2023.

Adverse events of grade 3-5 severity

Table 26: Grade 3-5 Adverse Events with a Difference in Incidence Rate of at Least 2% Between Treatment Arms, Safety-Evaluable Patients (ALINA)

MedDRA System Organ Class MedDRA Preferred Term	Alectinib (N=128)	Chemotherapy (N=120)
Investigations		
Neutrophil count decreased	0	12 (10.0%)
Blood creatine phosphokinase increased	8 (6.3%)	1 (0.8%)
White blood cell count decreased	0	4 (3.3%)
Gastrointestinal disorders		
Nausea	0	5 (4.2%)
Infections and infestations		
Appendicitis	4 (3.1%)	0
Blood and lymphatic system disorders		
Neutropenia	0	10 (8.3%)
General disorders and administration site conditions		
Asthenia	0	3 (2.5%)

Investigator text for AEs encoded using MedDRA version 26.0. Grading based on NCI CTCAE 5.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. Includes AEs with onset from first dose of study drug. Protocol: BO40336. Snapshot Date: 03AUG2023, Clinical Data Cut-off Date: 26JUN2023.

Adverse events suspected to be study treatment related

The proportion of patients with AEs suspected to be study treatment related was comparable between the alectinib arm (93.8%) and the chemotherapy arm (89.2%) (results not shown).

The following frequencies of treatment related AEs were observed in the alectinib arm of ALINA: AST increase (41.4%), CPK increase (43.0%), ALT increase (33.6%), bilirubin increase (33.6%), ALP (25.0%) increase, creatinine increase (14.8%), weight increase (14.8%), myalgia (28.1%), rash (14.1%), dysgeusia (10.2%) and bradycardia (7.8%).

Hy's law

One patient in the alectinib arm fulfilled the laboratory criteria suggestive of Hy's law (post-baseline ALT and AST >3 x ULN in combination with an elevated total bilirubin [>2 x ULN]). This patient presented with elevated ALT, AST, and bilirubin on Study Day 43. AEs of ALT and AST increased, both considered related to alectinib treatment by the investigator, were recorded. Both AEs were Grade 2, non-serious, resulted in alectinib treatment interruption, and resolved within 3 and 4 days of onset, respectively. While the patient meets the criteria for potential Hy's law, the presence of concomitant Gilbert`s syndrome and elevated AST and ALT levels serve as significant confounding factors, preventing the confirmation of this case as Hy's law.

Serious adverse event/deaths/other significant events

Serious adverse events

Table 27: Serious Adverse Events, Safety-Evaluable Patients (ALINA)

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%)

Investigator text for AEs encoded using MedDRA version 26.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same SAE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. Includes AEs with onset from first dose of study drug. Snapshot Date: 03AUG2023, Clinical Data Cut-off Date: 26JUN2023.

Deaths

No deaths were reported during alectinib-treatment in the ALINA study. Two patients (1.6%) died due to disease recurrence during the follow-up period (one within 30 days of last study drug administration).

Laboratory findings

Table 28: Summary of Clinically Relevant Shifts from Baseline in Laboratory Safety Parameters (ALINA)

Laboratory Test	Direction of Abnormality	Alectinib (N=128)	Chemotherapy (N=120)
Chemistry			
Albumin	Low	0/128	0/120
Alkaline Phosphatase	High	0/128	0/120
SGPT/ALT	High	3/128 (2.3%)	0/120
SGOT/AST	High	1/128 (0.8%)	0/120
Calcium	Low	0/127	0/120
	High	0/128	0/120
Creatine Kinase	High	10/128 (7.8%)	2/120 (1.7%)
Creatinine	High	0/128	0/120
Glucose, Fasting	Low	0/123	0/108
Gamma Glutamyl Transferase	High	0/128	1/120 (0.8%)
Glucose	Low	0/ 52	0/ 47
Magnesium	Low	0/128	0/117
	High	3/126 (2.4%)	0/115
Potassium	Low	0/128	0/120
	High	1/128 (0.8%)	0/120
Sodium	Low	1/128 (0.8%)	0/120
	High	0/128	0/120
Bilirubin	High	3/128 (2.3%)	0/120
Uric Acid	High	39/113 (34.5%)	23/114 (20.2%)
Coagulation			
International Normalized Ratio	High	0/125	1/118 (0.8%)
Activated Partial Thromboplastin Time	High	0/124	0/115
Hematology			
Hemoglobin	Low	0/128	1/120 (0.8%)
	High	0/128	0/120
Lymphocytes Abs	Low	3/128 (2.3%)	0/120
	High	0/128	0/120
Neutrophils, Total, Abs	Low	0/128	25/120 (20.8%)
Platelet	Low	0/128	0/120
Total Leukocyte Count	Low	0/128	8/120 (6.7%)
	High	0/128	0/120

For each patient, baseline is the last observation prior to initiation of study drug. For each laboratory test, patients with at least 1 post-baseline grade are included in the analysis. For each cell, the denominator is the number of patients with baseline NCI-CTCAE Grade 0-2 in the specified direction of abnormality, or Grade 1-4 in the opposite direction of abnormality. Patients with missing baseline values are included in the denominator. Snapshot Date: 03AUG2023, Clinical Data Cut-off Date: 26JUN2023. Note: CTCAE v5.0 grading for uric acid includes a clinical assessment component: Grade 1 is defined as '>ULN without physiologic consequences', Grade 2 is not defined, and Grade 3 is defined as '>ULN with physiologic consequences'. Any increase above ULN for uric acid was categorized as Grade 3; however, no patient with blood uric acid levels above the ULN reported Grade 3 AEs of hyperuricemia or blood uric acid increased.

Intrinsic factors

Age

Table 29: Overview of Adverse Events by Age (<65 Years vs. ≥65 Years), Safety-Evaluable Patients (ALINA)

	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%)

Investigator text for AEs encoded using MedDRA version 26.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately. Includes AEs with onset from first dose of study drug. Data cutoff: BO40336: 26JUN2023.

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): creatinine increase (10.9% and 29.6%), constipation (38.6% and 55.6%), weight increased (16.8% and 0), ALP increased (21.8% and 37.0%).

Race

Table 30: Overview of Adverse Events by Race (Asian vs. non-Asian), Safety-Evaluable Patients (ALINA)

	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%)

Investigator text for AEs encoded using MedDRA version 26.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately. Includes AEs with onset from first dose of study drug. Data cutoff: BO40336: 26JUN2023.

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

Sex

Table 31: Overview of Adverse Events by Sex, Safety-Evaluable Patients (ALINA)

	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%)

Investigator text for AEs encoded using MedDRA version 26.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately. Includes AEs with onset from first dose of study drug. Data cu-toff: BO40336: 26JUN2023.

AEs with notable differences (> 15%) between male and female patients were anaemia and blood AST increase. Compared with male patients, female patients more often experienced anaemia (33.8% vs 9.3%) and AST increase (48.6% vs 31.5%).

Disease stage

Table 32: Overview of Adverse Events by Stage (Stage IB, Stage II and Stage IIIA), Safety-Evaluable Patients (ALINA)

	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%)

Investigator text for AEs encoded using MedDRA version 26.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately. Includes AEs with onset from first dose of study drug. Data cutoff: BO40336: 26JUN2023.

The AEs by PT with notable differences ($\geq$20%) between patients with any two stages of NSCLC in the alectinib arm were (Stage IB, Stage II, and Stage IIIA, respectively):

- AST increased (17.6%, 47.6%, and 43.5%)
- Anaemia (0, 26.2%, and 27.5%)
- Blood CPK increased (23.5%, 40.5%, and 49.3%)
- COVID-19 (11.8%, 26.2%, and 34.8%)

Safety in special populations

Safety in elderly patients was presented in Table 29.

Only three patients with moderate renal impairment were included in the ALINA study. Dose modification or interruption due to AEs were more often reported among patient with mild renal impairment compared with patients with normal renal function. However, no significant difference in the safety profile of alectinib between patients with normal renal function and patients with mild renal impairment was observed (data not shown).

No patients with hepatic impairment were included in the ALINA and, hence, safety data in this special population is not available.

Discontinuation due to adverse events

Discontinuation due to adverse events

Table 33: Adverse events leading to treatment discontinuation in the ALINA study

	Alectinib (N=128)	Chemotherapy (N=120)
AEs by SOC (≥ 2% of patients in either arm)		
Investigations	3 (2.3%)	3 (2.5%)
General disorders and administration site conditions	0	5 (4.2%)
Gastrointestinal disorders	0	4 (3.3%)
Respiratory, thoracic and mediastinal disorders	3 (2.3%)	1 (0.8%)
Ear and labyrinth disorders	0	3 (2.5%)
AEs by PT (≥ 1% of patients in either arm)		
Nausea	0	4 (3.3%)
Asthenia	0	3 (2.5%)
Pneumonitis	3 (2.3%)	0
Blood creatinine increased	1 (0.8%)	2 (1.7%)
Fatigue	0	2 (1.7%)
vomiting	0	2 (1.7%)
tinnitus	0	2 (1.7%)

Adverse events leading to dose interruptions

Table 34: Adverse events leading to dose interruptions in the ALINA study

	Alectinib (N=128)	Chemotherapy (N=120)
AEs by SOC (≥ 3% of patients in either arm)		
Investigations	16 (12.5%)	8 (6.7%)
Infections and infestations	12 (9.4%)	2 (1.7%)
Gastrointestinal disorders	8 (6.3%)	3 (2.5%)
Blood and lymphatic system disorders	1 (0.8%)	8 (6.7%)
Musculoskeletal and connective tissue disorders	5 (3.9%)	0
General disorders and administration site conditions	4 (3.1%)	0
AEs by PT (≥ 3% of patients in either arm)		
ALT increased	7 (5.5%)	0
Blood CPK increased	7 (5.5%)	0
Neutrophil count decreased	0	6 (5.0%)
Neutropenia	0	6 (5.0%)
AST increased	6 (4.7%)	0
COVID-19	6 (4.7%)	1 (0.8%)
Blood bilirubin increased	5 (3.9%)	0

Adverse events leading to dose adjustment

Table 35: Adverse events leading to dose adjustment in the ALINA study

	Alectinib (N=128)	Chemotherapy (N=120)
AEs by SOC (≥ 3% of patients in either arm)		
Investigations	16 (12.5%)	4 (3.3%)
Gastrointestinal disorders	2 (1.6%)	4 (3.3%)
Skin and subcutaneous tissue disorders	5 (3.9%)	0
Blood and lymphatic system disorders	0	4 (3.3%)
AEs by PT (≥ 3% of patients in either arm)		
Blood CPK increased	8 (6.3%)	0
Blood bilirubin increased	5 (3.9%)	0
Nausea	0	4 (3.3%)

The most reported AEs (with incidence of >2%) that required alectinib dose reduction were increased blood CPK (6.3%) and increased blood bilirubin (3.9%).

Comparison of safety profiles: Adjuvant vs. aNSCLC populations

In addition to ALINA, pooled safety data for the following populations were provided to support the safety evaluation of alectinib:

- mNSCLC Population (N=405): alectinib-treated patients in Studies s NP28761 and NP28673 (N= 253 combined) and BO28984 (N= 152).
- Overall Pooled Safety Population (N=533): Alectinib-treated patients in Studies ALINA, NP28761, NP28673, and BO28984

The pooled safety data used to reflect the safety profile of alectinib 600 mg twice daily in the SmPC was the Overall Pooled Safety Population (N=533).

Overview of adverse events

Table 36: Overview of Adverse Events (ALINA and aNSCLC Population)

	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%)

Investigator text for AEs encoded using MedDRA version 26.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately. Includes AEs with onset from first dose of study drug. Data cutoff: BO28984: 29NOV2019, NP28673: 27OCT2017, NP28761: 12OCT2017, BO40336: 26JUN2023.

Adverse events

Table 37: Adverse Events with an Incidence Rate of at Least 10% in Either Group (ALINA and aNSCLC Population)

MedDRA System Organ Class MedDRA Preferred Term	Alectinib 600mg BID: BO40336 (N=128)	Alectinib 600mg BID: NP28761, NP28673, BO28984 (N=405)	Alectinib 600mg BID: NP28761, NP28673, BO28984, BO40336 (N=533)
Gastrointestinal disorders			
Constipation	54 (42.2%)	152 (37.5%)	206 (38.6%)
Diarrhoea	16 (12.5%)	77 (19.0%)	93 (17.4%)
Nausea	10 (7.8%)	83 (20.5%)	93 (17.4%)
Vomiting	9 (7.0%)	55 (13.6%)	64 (12.0%)
General disorders and administration site conditions			
Fatigue	18 (14.1%)	120 (29.6%)	138 (25.9%)
Oedema peripheral	13 (10.2%)	103 (25.4%)	116 (21.8%)
Asthenia	14 (10.9%)	53 (13.1%)	67 (12.6%)
Investigations			
Aspartate aminotransferase increased	53 (41.4%)	68 (16.8%)	121 (22.7%)
Blood bilirubin increased	43 (33.6%)	66 (16.3%)	109 (20.5%)
Alanine aminotransferase increased	43 (33.6%)	64 (15.8%)	107 (20.1%)
Blood creatine phosphokinase increased	55 (43.0%)	47 (11.6%)	102 (19.1%)
Weight increased	17 (13.3%)	51 (12.6%)	68 (12.8%)
Blood alkaline phosphatase increased	32 (25.0%)	26 (6.4%)	58 (10.9%)
Blood creatinine increased	19 (14.8%)	33 (8.1%)	52 (9.8%)
Musculoskeletal and connective tissue disorders			
Myalgia	36 (28.1%)	92 (22.7%)	128 (24.0%)
Arthralgia	10 (7.8%)	76 (18.8%)	86 (16.1%)
Back pain	7 (5.5%)	65 (16.0%)	72 (13.5%)
Infections and infestations			
Upper respiratory tract infection	9 (7.0%)	61 (15.1%)	70 (13.1%)
COVID-19	37 (28.9%)	0	37 (6.9%)
Respiratory, thoracic and mediastinal disorders			
Cough	19 (14.8%)	68 (16.8%)	87 (16.3%)
Dyspnoea	13 (10.2%)	59 (14.6%)	72 (13.5%)
Nervous system disorders			
Headache	14 (10.9%)	70 (17.3%)	84 (15.8%)
Dizziness	9 (7.0%)	46 (11.4%)	55 (10.3%)
Dysgeusia	13 (10.2%)	13 (3.2%)	26 (4.9%)
Skin and subcutaneous tissue disorders			
Rash	18 (14.1%)	57 (14.1%)	75 (14.1%)
Metabolism and nutrition disorders			
Decreased appetite	7 (5.5%)	42 (10.4%)	49 (9.2%)
Blood and lymphatic system disorders			
Anaemia	30 (23.4%)	84 (20.7%)	114 (21.4%)
Injury, poisoning and procedural complications			
Product dose omission issue	21 (16.4%)	0	21 (3.9%)
Product dose omission in error	16 (12.5%)	0	16 (3.0%)
Psychiatric disorders			
Insomnia	4 (3.1%)	45 (11.1%)	49 (9.2%)

Investigator text for AEs encoded using MedDRA version 26.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. Includes AEs with onset from first dose of study drug. Data cutoff: BO28984: 29NOV2019, NP28673: 27OCT2017, NP28761: 12OCT2017, BO40336: 26JUN2023.

Selected adverse events

Table 38: Selected Adverse Events (ALINA and aNSCLC Population)

	Alectinib 600mg BID: BO40336 (N=128)					Alectinib 600mg BID: NP28761, NP28673, BO28984 (N=405)				
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%)	377 (93.1%)	107 (26.4%)	40 (9.9%)	28 (6.9%)	109 (26.9%)
Gastrointestinal Tract Adverse Events	87 (68.0%)	4 (3.1%)	2 (1.6%)	0	9 (7.0%)	262 (64.7%)	17 (4.2%)	9 (2.2%)	1 (0.2%)	28 (6.9%)
Muscular Adverse Events, CPK Elevations	92 (71.9%)	8 (6.3%)	0	0	17 (13.3%)	218 (53.8%)	22 (5.4%)	5 (1.2%)	0	19 (4.7%)
Hepatocellular or Cholestatic Damage AEs or Abnormal Liver Function Tests	78 (60.9%)	6 (4.7%)	0	2 (1.6%)	18 (14.1%)	146 (36.0%)	39 (9.6%)	10 (2.5%)	18 (4.4%)	47 (11.6%)
Skin Disorders	50 (39.1%)	2 (1.6%)	0	0	6 (4.7%)	161 (39.8%)	5 (1.2%)	2 (0.5%)	0	9 (2.2%)
Hematologic Abnormalities	34 (26.6%)	1 (0.8%)	0	0	1 (0.8%)	113 (27.9%)	24 (5.9%)	5 (1.2%)	1 (0.2%)	9 (2.2%)
Oedema	20 (15.6%)	0	0	0	0	132 (32.6%)	4 (1.0%)	1 (0.2%)	1 (0.2%)	3 (0.7%)
Abnormal Renal Function	27 (21.1%)	1 (0.8%)	0	1 (0.8%)	3 (2.3%)	90 (22.2%)	10 (2.5%)	8 (2.0%)	5 (1.2%)	12 (3.0%)
Vision Disorders	12 (9.4%)	0	0	0	0	72 (17.8%)	4 (1.0%)	1 (0.2%)	0	2 (0.5%)
Bradycardia	15 (11.7%)	0	0	0	3 (2.3%)	44 (10.9%)	0	0	0	4 (1.0%)
Dysgeusia	17 (13.3%)	0	0	0	1 (0.8%)	22 (5.4%)	1 (0.2%)	0	0	0
Interstitial Lung Disease	4 (3.1%)	1 (0.8%)	1 (0.8%)	3 (2.3%)	0	6 (1.5%)	1 (0.2%)	3 (0.7%)	2 (0.5%)	2 (0.5%)

Selected Adverse Events	Alectinib 600mg BID: NP28761, NP28673, BO28984, BO40336 (N=533) 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	498 (93.4%)	129 (24.2%)	43 (8.1%)	34 (6.4%)	156 (29.3%)
Gastrointestinal Tract Adverse Events	349 (65.5%)	21 (3.9%)	11 (2.1%)	1 (0.2%)	37 (6.9%)
Muscular Adverse Events, CPK Elevations	310 (58.2%)	30 (5.6%)	5 (0.9%)	0	36 (6.8%)
Hepatocellular or Cholestatic Damage AEs or Abnormal Liver Function Tests	224 (42.0%)	45 (8.4%)	10 (1.9%)	20 (3.8%)	65 (12.2%)
Skin Disorders	211 (39.6%)	7 (1.3%)	2 (0.4%)	0	15 (2.8%)
Hematologic Abnormalities	147 (27.6%)	25 (4.7%)	5 (0.9%)	1 (0.2%)	10 (1.9%)
Oedema	152 (28.5%)	4 (0.8%)	1 (0.2%)	1 (0.2%)	3 (0.6%)
Abnormal Renal Function	117 (22.0%)	11 (2.1%)	8 (1.5%)	6 (1.1%)	15 (2.8%)
Vision Disorders	84 (15.8%)	4 (0.8%)	1 (0.2%)	0	2 (0.4%)
Bradycardia	59 (11.1%)	0	0	0	7 (1.3%)
Dysgeusia	39 (7.3%)	1 (0.2%)	0	0	1 (0.2%)
Interstitial Lung Disease	10 (1.9%)	2 (0.4%)	4 (0.8%)	5 (0.9%)	2 (0.4%)

Investigator text for AEs encoded using MedDRA version 26.0. All counts represent patients. Multiple occurrences of the same AE in one individual are counted only once.
Data cutoff: BO28984: 29NOV2019, NP28673: 27OCT2017, NP28761: 12OCT2017, BO40336: 26JUN2023.

Adverse events of grade 3-5 severity

Table 39: Grade 3-5 Adverse Events with an Incidence Rate of at Least 2% in Either Group (ALINA and aNSCLC Population)

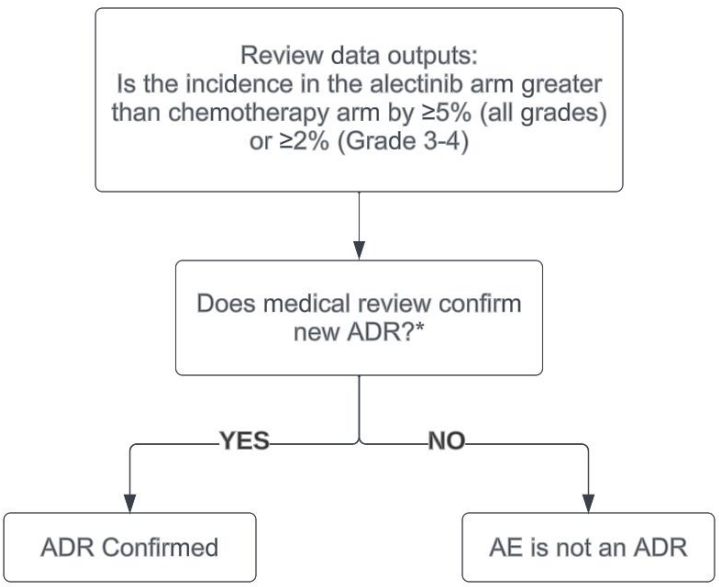
MedDRA System Organ Class MedDRA Preferred Term	Alectinib 600mg BID: BO40336 (N=128)	Alectinib 600mg BID: NP28761, NP28673, BO28984 (N=405)	Alectinib 600mg BID: NP28761, NP28673, BO28984, BO40336 (N=533)
Investigations			
Blood creatine phosphokinase increased	8 (6.3%)	15 (3.7%)	23 (4.3%)
Alanine aminotransferase increased	2 (1.6%)	15 (3.7%)	17 (3.2%)
Aspartate aminotransferase increased	1 (0.8%)	15 (3.7%)	16 (3.0%)
Blood bilirubin increased	2 (1.6%)	10 (2.5%)	12 (2.3%)
Infections and infestations			
Pneumonia	3 (2.3%)	13 (3.2%)	16 (3.0%)
Appendicitis	4 (3.1%)	1 (0.2%)	5 (0.9%)
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	1 (0.8%)	10 (2.5%)	11 (2.1%)
Blood and lymphatic system disorders			
Anaemia	0	17 (4.2%)	17 (3.2%)

Investigator text for AEs encoded using MedDRA version 26.0. Grading based on NCI CTCAE 5.0 for study BO40336 and NCI CTCAE 4.0 for studies BO28984, NP28673 and NP28761. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. Includes AEs with onset from first dose of study drug. Data cutoff: BO28984: 29NOV2019, NP28673: 27OCT2017, NP28761: 12OCT2017, BO40336: 26JUN2023.

Median time to Grade ≥ 3 CPK elevation was 15 days across clinical trials (BO40336, BO28984, NP28761, NP28673).

Adverse drug reactions

Methodology for selection of ADRs



ADR = adverse drug reaction; AE=adverse event. *Based on medical judgement, a decision may be made to include terms that have not met any of the pre-defined criteria, or not to include terms that have met one or more

numerical criteria. Medical judgment includes knowledge of biological plausibility, known alectinib safety profile, experience with similar in-class agents, relevant non-clinical data, exclusion of alternate causes, and general knowledge of human pathophysiology.

Figure 17: Methodology for ADR Identification in ALINA

Table 40: ADRs reported in alectinib clinical trials (BO40336, BO28984, NP28761, NP28673; N=533)

System organ class ADRs (MedDRA)	**Alecensa N=533**	
	Frequency category (all grades)	**Frequency category (grades 3-4)**
Blood and lymphatic system disorders		
Anaemia[1)]	Very common	Common
Haemolytic anaemia[2)]	Common	-*
Nervous system disorders		
Dysgeusia[3)]	Common	Uncommon
Eye disorders		
Vision disorders[4)]	Common	-*
Cardiac disorders		
Bradycardia[5)]	Very common	-*
Respiratory, thoracic and mediastinal disorders		
Interstitial lung disease / pneumonitis	Common	Uncommon
Gastrointestinal disorders		
Diarrhoea	Very common	Uncommon
Vomiting	Very common	Uncommon
Constipation	Very common	Uncommon
Nausea	Very common	Uncommon
Stomatitis[6)]	Common	Uncommon
Hepatobiliary disorders		
Increased AST	Very common	Common
Increased ALT	Very common	Common
Increased bilirubin[7)]	Very common	Common
Increased alkaline phosphatase	Very Common	Uncommon
Drug-induced liver injury[8)]	Uncommon	Uncommon
Skin and subcutaneous tissue disorders		
Rash[9)]	Very common	Common
Photosensitivity	Common	Uncommon
Musculoskeletal and connective tissues disorders		
Myalgia[10)]	Very common	Uncommon
Increased blood creatine phosphokinase	Very common	Common
Renal and urinary disorders		
Acute kidney injury	Uncommon	Uncommon**
Blood creatinine increased	Common	Uncommon**
General disorders and administration site conditions		
Oedema[11)]	Very common	Uncommon
Investigations		
Weight increased	Very common	Uncommon
Metabolism and Nutrition Disorders		
Hyperuricaemia[12)]	Common	-*

* No Grade 3-4 ADRs were observed.
** Includes one Grade 5 event (observed in the advanced NSCLC setting).
[1)] includes cases of anaemia, haemoglobin decreased and normochromic normocytic anaemia.
[2)] cases reported in study BO40336 (N=128).
[3)] includes cases of dysgeusia, hypogeusia, and taste disorder.

[4)] includes cases of blurred vision, visual impairment, vitreous floaters, reduced visual acuity, asthenopia, diplopia, photophobia, and photopsia.
[5)] includes cases of bradycardia and sinus bradycardia.
[6)] includes cases of stomatitis and mouth ulceration.
[7)] includes cases of blood bilirubin increased, hyperbilirubinaemia, bilirubin conjugated increased, and blood bilirubin unconjugated increased.
[8)] includes two patients with reported MedDRA term of drug-induced liver injury as well as one patient with reported Grade 4 increased AST and ALT who had documented drug-induced liver injury by liver biopsy.
[9)] includes cases of rash, rash maculopapular, dermatitis acneiform, erythema, rash generalised, rash macular, rash pruritic, rash macular, exfoliative rash, and rash erythematous.
[10)] includes cases of myalgia, musculoskeletal pain, and arthralgia.
[11)] includes cases of oedema peripheral, oedema, generalised oedema, eyelid oedema, periorbital oedema, face oedema, localised oedema, peripheral swelling, face swelling, lip swelling, swelling, joint swelling and eyelid swelling.
[12)] includes cases of hyperuricaemia and increased blood uric acid.

Selected adverse drug reactions:

- Interstitial lung disease (ILD)/pneumonitis: Across clinical trials, ILD/pneumonitis occurred in 1.3% of patients treated with alectinib, 0.4% of these cases were Grade 3 and treatment discontinuations due to ILD/pneumonitis occurred in 0.9% of patients.

- Hepatotoxicity: Across clinical trials, three patients had a documented drug-induced liver injury (including two patients with the reported term drug-induced liver injury and one patient with reported Grade 4 increased AST and ALT who had documented drug-induced liver injury by liver biopsy). Adverse reactions of increased AST and ALT levels (22.7% and 20.1% respectively) were reported in patients treated with alectinib across clinical trials. The majority of these events were of Grade 1 and 2 intensity, and events of Grade ≥ 3 were reported in 3.0% and 3.2% of the patients for increased AST and ALT levels, respectively. The events generally occurred during the first 3 months of treatment, were usually transient and resolved upon temporary interruption of alectinib treatment (reported for 2.3% and 3.6% of the patients, respectively) or dose reduction (1.7% and 1.5%, respectively). In 1.1% and 1.3% of the patients, AST and ALT elevations, respectively, led to withdrawal from alectinib treatment. Adverse reactions of bilirubin elevations were reported in 25.1% of the patients treated with alectinib across clinical trials. The majority of the events were of Grade 1 and 2 intensity; Grade ≥ 3 events were reported in 3.4% of the patients. The events generally occurred during the first 3 months of treatment, were usually transient and the majority resolved upon dose modification. In 7.7% of patients, bilirubin elevations led to dose modifications and in 1.5% of patients, bilirubin elevations led to withdrawal from alectinib treatment.

- Bradycardia: Cases of bradycardia (11.1%) of Grade 1 or 2 have been reported in patients treated with alectinib across clinical trials. No patients had events of Grade ≥ 3 severity. There were 102 of 521 patients (19.6%) treated with alectinib, for whom serial ECGs were available, had post-dose heart rate values below 50 beats per minute (bpm).

- Severe myalgia and CPK elevations: Cases of myalgia (34.9%) including myalgia events (24.0%), arthralgia (16.1%), and musculoskeletal pain (0.9%) have been reported in patients treated with alectinib across clinical trials. The majority of events were Grades 1 or 2 and five patients (0.9%) had a Grade 3 event. Dose modifications of alectinib treatment due to these adverse events were required for nine patients (1.7%); alectinib treatment was not withdrawn due to these events of myalgia. Elevations of CPK occurred in 55.6% of 491 patients with CPK laboratory data available across clinical trials with alectinib. The incidence of Grade ≥ 3 elevations of CPK was 5.5%. Median time to Grade ≥ 3 CPK elevation was 15 days across trials. Dose modifications for elevation of CPK occurred in 5.3% of patients; withdrawal from alectinib treatment did not occur due to CPK elevations.

- Gastrointestinal effects: Constipation (38.6%), nausea (17.4%), diarrhoea (17.4%) and vomiting (12.0%) were the most commonly reported gastrointestinal (GI) reactions. Most of these events were of mild or moderate severity; Grade 3 events were reported for diarrhoea (0.9%), nausea (0.4%), vomiting (0.2%), and constipation (0.4%). These events did not lead to withdrawal from Alecensa treatment. Median time to onset for constipation, nausea, diarrhoea, and/or vomiting events across clinical trials was 21 days. The events declined in frequency after the first month of treatment.

2.5.1. Discussion on clinical safety

Alectinib as monotherapy was approved in 2017 for the treatment of adult patients with ALK-positive advanced NSCLC. The most common ADRs previously established for alectinib include anaemia, bradycardia, GI disorders, rash, hepatobiliary disorders (such as increased AST, ALT, bilirubin and alkaline phosphatase), myalgia, increased blood creatinine and weight gain.

It is noted that there are currently no safety concerns to be addressed in the RMP according to the latest approved version (3.3).

Given the low frequency of ALK positive NSCLC (4-5%), the safety data base coming from ALINA study (128 patients in the alectinib arm and 120 patients in the chemotherapy arm) is considered of an acceptable magnitude.

Summary of the overall safety data

Pivotal study BO40336 (acronym ALINA)

Exposure: Patients in the experimental arm received 600 mg alectinib orally BID (the approved posology), for a median of around 24 months (range: 0-25 months). The median dose intensity of alectinib was 99.4% (range: 47%-100%). Most patients (112 [87.5%]) had received alectinib ≥ 18 months. About 22% had received alectinib ≥ 24 months. Patients in the control arm received one of the protocol-specified platinum-based chemotherapy regimens which were administered for 4 cycles, with each cycle lasting 21 days. The median exposure to chemotherapy was 2.1 months. The median dose intensity was 100%, with 90.0% of patients completing 4 cycles of platinum-based chemotherapy. The data presented on patient exposure doesn't raise any concern.

Adverse events: 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. The proportion of patients who experienced at least one AE in the alectinib arm was comparable to the chemotherapy arm (98.4% and 93.3%, respectively). Grade 3-5 AEs are comparable between the study arms (29.7% and 30.8%, respectively). SAEs were more frequently reported in the alectinib arm (13.3%) compared with the comparator arm (8.3%). No AEs with fatal outcome was reported in either arm during the study. AEs leading to withdrawal from treatment were more common in the chemotherapy arm (11.7%) than in the alectinib arm (5.5%). However, AEs leading to dose modification/interruption were more frequently reported in the alectinib arm compared to the control arm (43.0% and 22.5%, respectively).

AEs wherein a higher proportion of alectinib-treated patients (>10% relative difference between groups) reported events included increased AST (+36.4%), increased blood CPK (+42.2%), increased ALT (+24.4%), increased blood bilirubin (+32.8%), increased blood ALP (+21.7%), constipation (+17.2%), weight increase (+12.5%), myalgia (+26.4%) and cough (+11.5%). These AEs are in line with the known safety profile of alectinib.

Selected AEs: The proportion of patients reporting any selected adverse event was 94.5% in the alectinib arm and 89.2% in the chemotherapy arm. These were more often Grade ≥3 in the

chemotherapy arm (27.5%) than in the alectinib arm (17.2%). In the alectinib arm, 2.3% of these selected AEs were judged serious compared with 5.8% in the chemotherapy arm.

Selected AEs lead to treatment discontinuation more often in the chemotherapy arm (8.3%) than in the alectinib arm (4.7%). Dose reductions or interruptions were however more frequent in the alectinib arm (36.7% vs 20.0%).

The following selected adverse events were more commonly reported in the alectinib arm compared with the chemotherapy arm: muscular AEs (including CPK elevation, 71.9% vs 10.0%), hepatobiliary toxicity (hepatocellular, cholestatic damage AEs or abnormal liver function tests, 60.9% and 13.3%), skin disorders (39.1% vs 18.3%), abnormal renal function (21.1% vs 14.2%), dysgeusia (13.3% vs 3.3%), oedema (15.6% vs 1.7%), bradycardia (11.7% vs 0%), vision disorders (9.4% vs 2.5%) and interstitial lung disease (3.1% vs 0%). These AEs are in line with the known safety profile of alectinib.

The proportion of patients who reported at least one AE related to hematologic abnormalities was 26.6% in the alectinib arm and 46.7% in the chemotherapy arm. The most frequently reported AE by PT was anaemia in both treatment arms (23.4% in the alectinib arm vs. 25.8% in chemotherapy arm).

AEs of G3-5: In terms of severity, the proportion of patients that experienced at least one Grade 3-5 AE in the alectinib arm was comparable to the chemotherapy arm (29.7% and 30.8%, respectively). The most common grade $\geq$3 AEs in the alectinib arm was increased blood CPK (6.3%) and appendicitis (3.1%).

AEs suspected to be study treatment related: These AEs are all adjudicated as ADRs of alectinib and addressed in the SmPC.

Hy's law: Drug-induced liver injury is listed as an uncommon ADR of alectinib treatment in sections 4.4 and 4.8 of the SmPC.

Serious AEs: SAEs were more frequently reported in the alectinib arm (13.3%) compared with the comparator arm (8.3%). The most frequently reported SAEs ($\geq$ 3 patients) were appendicitis (3.1%) and pneumonia (2.3%). Most SAEs were Grade 3 or less in severity and had resolved by the CCOD. The frequency of treatment discontinuations due to SAEs was low in both the alectinib arm (0.8%) and the chemotherapy arm (3.3%). As were the frequency of dose modifications due to SAEs (5.5% and 3.3% in the alectinib arm and chemotherapy arm, respectively). SAEs lead to withdrawal from treatment for one patient in the alectinib arm (0.8%) and 4 patients (3.3%) in the chemotherapy arm. SAEs lead to dose modification or interruptions in 5.5% of patients in the alectinib arm and 3.3% of patients in the chemotherapy arm. Treatment related SAEs were more commonly reported in the chemotherapy arm (6.7% vs 1.6%).

Laboratory findings: No concerns have been evoked in terms of laboratory findings.

Intrinsic factors:

Age: The total number of AEs and related AEs during alectinib treatment did not differ with age. There was however a difference observed in proportion of Grade >3 AEs (27.7% vs 37.0%) and SAEs (11.9% vs 18.5%), with patients > 65 years being more prone to these events compared with patients < 65 years. This is in general not unexpected.

Patients < 65 years less frequently experiences AEs leading to withdrawal from treatment (2% compared with 18% for patients > 65 years).

Of note, the vast majority (78.9%) of the alectinib-treated patients were <65 years.

Race: The incidence of SAEs was comparable between Asian (14.3%) and non-Asian patients (12.1%).

Asian patients more frequently experienced AEs leading to dose modifications or interruptions compared with non-Asian patients (48.6% vs 36.2%). Non-Asian patients more frequently experienced AEs leading to withdrawal from treatment compared with Asian patients (8.6% vs 2.9%).

Sex: Proportion of patients experiencing AEs (100% vs 96.3%) and SAEs (13.5% vs 13.0%) were comparable between females and males. AEs leading to dose modifications or interruptions was more common among male participants (7.4%) compared with female (4.1%) whereas females more often experienced AE leading to withdrawal from treatment (6.8% vs 3.7%).

Disease stage: In the alectinib arm, the proportion of patients who experienced Grade 3–5 AEs was lower in patients with Stage II (23.9%) compared with patients with Stage IB (35.7%) and Stage IIIA (32.4%). The proportion of patients who experienced SAEs was comparable across disease Stages IB and IIIA (Stage IB: 14.3% and Stage IIIA: 14.7%) and slightly less in Stage II (10.9%).

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 (57.1%) compared with patients with Stage II (32.6%) and Stage IIIA (47.1%).

As the subgroups are small and differ in size (Stage IB: 14 patients, Stage II: 46 patients, Stage IIIA: 68 patients) conclusions cannot be drawn.

Special populations: Only three patients with moderate renal impairment were included in the ALINA study and no conclusions can be drawn from this subgroup.

No patients with hepatic impairment were included in the ALINA and, hence, safety data in this special population is not available. The results of study NP29783, evaluating the effect of hepatic impairment on the pharmacokinetics of alectinib, are included in the SmPC section 5.2.

Discontinuation due to AEs: AEs leading to study treatment discontinuation were less commonly reported in the alectinib arm (5.5%) compared with the chemotherapy arm (11.7%). This frequency is considered low. In the alectinib arm, the most reported AE leading to treatment discontinuation was pneumonitis (2.3%). 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 the chemotherapy arm (10.0% and 18.3%, respectively). The MAH claims that a possible explanation is the longer duration of treatment in patients receiving alectinib as well as different dose schedules. The explanation is reasonable.

Comparison of the alectinib safety profile in the adjuvant setting (ALINA) vs advanced NSCLC

Adverse events: The incidence of most AEs was comparable or higher in the aNSCLC Population compared with the alectinib arm of ALINA, except for the following that were all more frequently reported within the ALINA study: AST increase (41.4% vs 16.8%), ALT increase (33.6% vs 15.8%), blood bilirubin increase (33.6% vs 16.3%), blood ALP increase (25.0% vs 6.4%), blood CPK increase (43.0% vs 11.6%), blood creatinine increase (14.8% vs 8.1%), and dysgeusia (10.2% vs 3.2%). These events are identified ADRs for alectinib. Most patients with ALT, AST or bilirubin elevations experienced the first onset within the first 3 months of treatment. In both the ALINA and the aNSCLC populations, the majority of patients with ALT, AST or bilirubin elevations experienced the first onset within the first 3 months of treatment.

Hepatobiliary toxicity (data not shown) was rarely of Grade $\geq$ 3 in the ALINA study (0.8-1.6%) but occurred more frequently in the adjuvant population. Based on the ALINA trial, the frequency category of increased ALP has been upgraded from “common” to “very common”.

Blood CPK is listed as a common ADR in section 4.8 of the SmPC. Blood CPK increase were more often of Grade ≥ 3 in the ALINA study compared with in the aNSCLC population (6.3% vs 3.7%, data not shown). No changes are proposed in the SmPC as Grade 3 CPK increase already has frequency category "common".

The incidence of renal disorder (increased creatinine) was higher among patients receiving alectinib in the adjuvant setting compared with the advanced population. Creatinine increase is already listed as a common ADR in section 4.8 of the SmPC.

Selected adverse events: The same alectinib dosing (600 mg BID) was used in the ALINA study and in the aNSCLC population, but therapy was ongoing for a longer period in the ALINA study (median duration of exposure 23.9 months compared with 14.8 months in the advanced cohort). The total number of patients with at least one selected AE was comparable in the two cohorts, but the following three categories were more frequently reported in the ALINA study: muscular AEs and CPK elevations (71.9% vs 53.8%), hepatocellular or cholestatic damage AE or abnormal liver function test (60.9% vs 36.0%) and dysgeusia (13.3% vs 5.4%). Vision disorder was more frequently reported in the aNSCLC population (17.8%) compared with the alectinib arm of ALINA (9.4%) and the frequency category has been updated from "very common" to "common" in section 4.8 of the SmPC. Grade ≥3 AEs and SAEs were less frequently reported in the adjuvant ALINA cohort.

AEs of G3-5: In the aNSCLC population, the proportion of alectinib-treated patients who experienced Grade 3–5 AEs was 46.7% (compared with 29.7% in the alectinib arm of ALINA). The most frequently reported grade ≥ 3 AEs (with incidence of > 2%) in ALINA were increased blood CPK (6.3%), appendicitis (3.1%) and pneumonia (2.3%). Blood CPK increases were more frequently of grade ≥ 3 in ALINA compared with the aNSCLC population (3.7%). In the aNSCLC population, anaemia was the most reposted grade ≥ 3 AE (4.2%). In the adjuvant population no patient experienced grade ≥ 3 anaemia. The proportion of patients who experienced AEs leading to alectinib dose reduction was higher in the adjuvant ALINA cohort (25.8%) compared with the advanced population (16.0%, Summary of Clinical Safety Body, Table 27, data not shown). Increased CPK was a common reason for dose reduction in the alectinib arm of ALINA (6.3%) but less common in the aNSCLC population (1.5%).

Treatment interruptions: In terms of treatment interruptions, the alectinib arm of ALINA was comparable to the aNSCLC population (27.3% and 30.4%, respectively, data not shown). Reasons for interruptions did however differ between the two alectinib treated populations, with the following AEs more commonly leading to interruption in the adjuvant ALINA cohort: AST increase (4.7% vs 1.5%), CPK increase (5.5% vs 2.2%), ALT (5.5% vs 3.0%).

The proportion of patients who experienced AEs leading to alectinib dose reduction was higher in the adjuvant patient population (25.8%) compared with the advanced population (16.0%). Increased CPK was the most common reason for dose reduction in the alectinib arm of ALINA (6.3%) (data not shown).

Dose modification or interruption due to AEs were more often reported in the adjuvant alectinib cohort compared to the aNSCLC population (43.0% and 35.8%, respectively).

Adverse drug reactions: The methodology for selection of ADRs appears acceptable. The most common ADRs previously established for alectinib include anaemia, bradycardia, GI disorders, rash, hepatobiliary disorders (such as increased AST, ALT, bilirubin, and alkaline phosphatase), myalgia, increased blood creatinine and weight gain. Based on the ALINA study, increased ALT and increased AST was added to the list of the most common ADRs (frequency ≥20%) in the SmPC. Hyperuricemia was observed for 12 patients (9.4%) in the alectinib arm and has been proposed by the MAH as a new ADR and to be added to the SmPC section 4.8. This was agreed.

2.5.2. Conclusions on clinical safety

The safety profile as characterised in the pivotal study is in line with what has previously been established for alectinib in the aNSCLC setting. Apart from `Hyperuricaemia´ added as a new ADR, no new safety concerns have been evoked based on the submitted data.

The safety profile is considered acceptable provided that efficacy has been established.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 4.2 with the following content:

Safety concerns

Table 41: List of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Carcinogenicity

Carcinogenicity has been included as missing information.

Pharmacovigilance plan

Table 42: Ongoing and planned additional pharmacovigilance activities

Study Status	**Summary of Objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
NA	NA	NA	NA	NA
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
N/A	N/A	N/A	N/A	N/A
Category 3 - Required additional pharmacovigilance activities				

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Study 724237 26 Weeks Oral Gavage Toxicity and Toxicokinetic Study in CByB6F1-Tg(HRAS)2Jic (rasH2 tg/wt, model 1178) Mouse (preliminary title; GLP study) Planned	Evaluate carcinogenic potential of alectinib in nonclinical carcinogenicity studies	*Missing Information:* Carcinogenicity	Final report submission (Report No. 1130532):	1st quarter 2027
Study 723267 104-Week Rat Carcinogenicity Study (preliminary title; GLP study) Planned	Evaluate carcinogenic potential of alectinib in nonclinical carcinogenicity studies	*Missing Information:* Carcinogenicity	Final report submission (Report No. 1130533):	4th quarter 2028

The newly added missing information carcinogenicity will be further investigated by tow category 3 post-authorisation studies, for which results are expected Q1 2027 and Q4 2028.

Risk minimisation measures

Table 43: Summary Table of Pharmacovigilance Activities and Risk-Minimization Activities by Safety Concern

Safety Concern	Risk-Minimization Measure(s)	Pharmacovigilance Activities
Missing Information		
Carcinogenicity	Routine risk-minimization measures: None Additional risk-minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study 724237 (final report Q1 2027) 26 Weeks Oral Gavage Toxicity and Toxicokinetic Study in CByB6F1-Tg(HRAS)2Jic (rasH2 tg/wt, model 1178) Mouse (preliminary title; GLP study) Study 723267 (final report Q4 2028) Study 723267 104-Week Rat Carcinogenicity Study (preliminary title; GLP study)

Routine risk minimisation measures are sufficient to mitigate carcinogenicity.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

There have not been revisions that significantly affect the overall readability and design of the package leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

New indication:

Alecensa as monotherapy is indicated as adjuvant treatment following complete tumour resection for adult patients with ALK-positive NSCLC at high risk of recurrence (see section 5.1 for selection criteria).

ALK fusions are found in approximately 4–5% of patients with NSCLC. ALK-positive NSCLCs are generally associated with young age, never- or light-smoking history, adenocarcinoma histology, and are associated with a high rate of brain metastases (~50-60% of patients over the course of their disease) (Zhang et al. 2016; Johung et al. 2016, Aldea et al 2020).

3.1.2. Available therapies and unmet medical need

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, and immunotherapy is generally not recommended in patients with ALK-positive disease. Therefore, for patients with resected ALK-positive NSCLC, adjuvant chemotherapy is still the standard of care (NCCN 2023, ESMO 2021).

Data from historical adjuvant studies showed that adjuvant chemotherapy provides limited benefit in the all-comer population with modest benefit for Stage IB patients (Pignon et al 2008), and no survival advantage specifically in Stage IB patients with tumours < 4 cm (Strauss et al. 2011). Since no benefit has been demonstrated with chemotherapy treatment, surgical resection without any adjuvant therapy remains the standard of care in this population (NCCN 2023, ESMO 2021). The long-term outcome nevertheless remains poor, with approximately 40-46% of patients suffering from cancer recurrence within the first 5 years after initial diagnosis, and only 60-73% remaining alive at 5 years (Chansky et al. 2017).

3.1.3. Main clinical studies

The ALINA study was 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 ALK-positive non-small-cell lung cancer. Two populations were analysed in this study, a subpopulation consisting of Stage II-IIIa and the ITT population also including stage IB (tumors ≥ 4 cm) with hierarchical control of the type I error. This assessment is based on data from the interim analysis with 59 and 65 events in the Stage II-IIIa subpopulation and the ITT population respectively.

3.2. Favourable effects

At the first interim analysis, the ALINA study met its primary endpoint, demonstrating improvement in DFS with alectinib over chemotherapy in two prespecified populations: the Stage II-IIIA (HR: 0.24;

95% CI: 0.13, 0.45; p value < 0.0001) and the ITT Population (Stage IB-IIIA; HR: 0.24; 95% CI: 0.13, 0.43; p value < 0.0001).

3.3. Uncertainties and limitations about favourable effects

DFS and OS data were immature at the time of the CCOD. Updated efficacy results will be submitted as a post authorisation efficacy study, as an Annex II condition.

3.4. Unfavourable effects

AEs wherein a higher proportion of alectinib-treated patients (>10% relative difference between groups) reported events included increased AST (+36.4%), increased blood CPK (+42.2%), increased ALT (+24.4%), increased blood bilirubin (+32.8%), increased blood ALP (+21.7%), constipation (+17.2%), weight increase (+12.5%), myalgia (+26.4%) and cough (+11.5%). These AEs are in line with the known safety profile of alectinib.

Hyperuricemia was observed for 12 patients (9.4%) in the alectinib arm and has been added as a new ADR to section 4.8 of the SmPC.

In terms of severity, the proportion of patients that experienced at least one Grade 3-5 AE in the alectinib arm was comparable to the chemotherapy arm (29.7% and 30.8%, respectively). The most common grade >3 AEs in the alectinib arm was increased blood CPK (6.3%), appendicitis (3.1%) and pneumonia (2.3%). No AEs with fatal outcome was reported in either arm during the study.

SAEs were more frequently reported in the alectinib arm (13.3%) compared with the comparator arm (8.3%). The most frequently reported SAEs (> 3 patients) were appendicitis (3.1%) and pneumonia (2.3%).

AEs leading to withdrawal from treatment were more common in the chemotherapy arm (12.5%) than in the alectinib arm (5.5%), however considered of an acceptable magnitude. In the alectinib arm, the most reported AE leading to treatment discontinuation was pneumonitis (2.3%).

3.5. Uncertainties and limitations about unfavourable effects

With a longer survival in this setting, there is a need to address the carcinogenic risk. The MAH will perform an ICH S1B compliant carcinogenicity program to be reported post-approval (2 post authorisation, non-clinical studies).

3.6. Effects Table

Table 44: Effects Table for Alectinib in resected ALK-positive NSCLC (data cut-off:).

Effect	Short description	Unit	Treatment	Control	Uncertainties	References
Favourable Effects						
			N=116	N=115		
DFS	Stage II-IIIA	Events (%)	14 (12)	45 (39)		
		HR (95%CI)	0.24 (0.13, 0.45)			
		p-value	<0.0001			
			N=130	N=127		
DFS	Stage IB-IIIA	Events (%)	15 (12)	50 (39)		
		HR (95%CI)	0.24 (0.13, 0.43)			
		p-value	<0.0001			

Effect	Short description	Unit	Treatment	Control	Uncertainties	References
Unfavourable Effects						
TEAEs	Any		98.4	93.3		
(≥7% difference in incidence between treatment arms)	AST increase ALT increase CPK increase Bilirubin increase Creatinine Hyperuricemia Myalgia Bradycardia		41.4 33.6 43.0 33.6 14.8 9.4 28.1 7.8	5.0 9.2 0.8 0.8 5.0 1.7 1.7 0		
Grade 3 and 4	Any		29.7	30.8		
SAEs	Any		13.3	8.3		
TEAEs leading to discontinuation	Any		5.5	11.7		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A relevant improvement in DFS has been demonstrated with alectinib as monotherapy over chemotherapy in patients at high risk of recurrence with completely resected ALK-positive non-small-cell lung cancer.

The safety profile as characterised in the pivotal study is in line with what has previously been established for alectinib in the aNSCLC setting. Apart from `Hyperuricaemia´ added as a new ADR, no new safety concerns have been evoked based on the submitted data. The safety profile is considered acceptable. With a longer survival in this setting, there is a need to address the carcinogenic risk. The MAH will perform an ICH S1B compliant carcinogenicity program to be reported post-approval. Since a relevant improvement in DFS has been demonstrated and available data are not suggestive of a carcinogenic potential, this approach is agreed.

3.7.2. Balance of benefits and risks

The balance of benefits and risks is positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Alencesa in the adjuvant setting is positive.

The following measures are considered necessary to address issues related to efficacy:

Post-authorisation efficacy study (PAES): In order to further evaluate the efficacy of Alecensa as monotherapy as adjuvant treatment following complete tumour resection for adult patients with Stage IB (≥ 4 cm) - IIIA ALK-postitive NSCLC, the MAH should submit the updated descriptive DFS, the descriptive OS results and the 5-year survival follow up results from the BO40336 study.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication to include the use of Alecensa as monotherapy in adult patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) as adjuvant treatment following tumour resection, based on final results from study BO40336 (ALINA), a randomized, active controlled, multicenter, open-label, Phase III study designed to evaluate the efficacy and safety of alectinib compared with platinum-based chemotherapy in the adjuvant setting in patients with completely resected Stage IB (tumours ≥4 cm) to Stage IIIA ALK-positive NSCLC. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.2 of the RMP has also been agreed. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and to introduce editorial changes to the PI. As part of the application, the MAH is requesting a 1-year extension of the market protection.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II, IIIA and IIIB and to the Risk Management Plan are recommended.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due Date
Post Authorisation Efficacy Study (PAES): In order to further evaluate the efficacy of Alecensa as monotherapy as adjuvant treatment following complete tumour resection for adult patients with Stage IB (≥ 4 cm) - IIIA ALK-postitive NSCLC, the MAH should submit the following results from the BO40336 study:	

• Updated descriptive DFS and descriptive OS results	Q3 2025
• 5-year survival follow up results	Q3 2027

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 1).