EU RISK MANAGEMENT PLAN FOR ALECENSA ®/ALECTINIB

RMP version to be assessed as part of this application:

RMP Version number: 4.2

Data lock point for this RMP: 11 April 2024

Date of final sign off: See latest date in date stamps below

Date and Time (UTC)	Reason for Signing	Name
25-Apr-2024 10:05:37	Deputy QPPV	PPD
25-Apr-2024 19:17:48	Company Signatory (PV)	

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Rationale for submitting an updated RMP:

The alectinib EU risk management plan (RMP) version 4.2 has been prepared to support the extension of the license of Alecensa to the adjuvant treatment in patients with ALK-positive NSCLC following tumor resection.

Additional changes were made in this RMP to provide the most updated information available. A summary of the significant changes from version 4.1 to 4.2 is presented below.

Summary of significant changes in this RMP

The document was updated throughout to reflect a change in description of the safety concern of missing information to “carcinogenicity” rather than “nonclinical data on carcinogenicity,” and to update the proposed indication to specify a target population with ALK-positive NSCLC at high risk of recurrence.

Minor editorial and formatting updates were made throughout, as needed.

Other RMP versions under evaluation: There are no other versions under evaluation.

Details of Currently Approved RMP: Version number: 3.3

Approved with procedure: EMEA/H/C/004164/II/0044

Date of approval (opinion date): 12 January 2023

See page 1 for signature and date

Dr. PPD (Deputy EU QPPV) Date

See page 1 for signature and date

PPD Date

PART I: PRODUCT OVERVIEW

Table 1 Product Overview

Active Substance(s) (INN or common name)	Alectinib
Pharmacotherapeutic group(s) (ATC Code)	L01ED03
Marketing Authorization Holder	Roche Registration Limited
Medicinal products to which this RMP refers	One
Invented name(s) in the European Economic Area (EEA)	Alecensa
Marketing authorization procedure	Centralized authorization procedure
Brief description of the product including:	Chemical Class: Protein Kinase inhibitor
	Summary of mode of action: Alectinib is a highly selective and potent anaplastic lymphoma kinase (ALK) and rearranged during transfection (RET) tyrosine kinase inhibitor.
	Important information about its composition: Each hard capsule contains alectinib hydrochloride as active ingredient and lactose monohydrate and sodium (as sodium lauryl sulfate) as excipients with known effect.
Hyperlink to the Product Information	Product Information
Indication(s) in the EEA	Current: **Treatment of Advanced Non-Small Cell Lung Cancer** Alecensa as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib. Alecensa as monotherapy is indicated for the first-line treatment of adult patients with ALK-positive advanced NSCLC.
	Proposed: **Adjuvant Treatment of Resected Non-Small Cell Lung Cancer** 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).

Dosage in the EEA	600 mg (four 150 mg capsules) taken twice daily with food (total daily dose of 1200 mg). 450 mg taken orally twice daily with food (total daily dose of 900 mg) for patients with underlying severe hepatic impairment.
Pharmaceutical form(s) and strengths	Current: White hard capsule of 19.2 mm length, with “ALE” printed in black ink on the cap and “150 mg” printed in black ink on the body. Each hard capsule contains alectinib hydrochloride equivalent to 150 mg alectinib.
	Proposed: Not applicable
Is or will the product be subject to additional monitoring in the EU?	No

ALK = anaplastic lymphoma kinase; mg = milligram; NSCLC = non-small cell lung cancer; RET = rearranged during transfection.

ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the concentration-time curve from time 0 to time infinity
$AUC_{0\text{-last}}$	Area under the concentration-time curve from time 0 to last measureable concentration
BCRP	Breast Cancer Resistance Protein
BID	Twice Daily
BOR	Best Overall Response
BP	Blood Pressure
C_{max}	Maximum Plasma Concentration Observed
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete Response
CrCL	Creatinine Clearance
CYP3A	Cytochrome P450 3A
DDI	Drug-drug interaction
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GD	Gestation days
GVP	Good Pharmacovigilance Practices
hERG	Human ether-à-go-go-related gene
IBD	International Birth Date
MAH	Marketing Authorization Holder
NOAEL	No Observed Adverse Effect Level
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
PFS	Progression-Free Survival
P-gp	P-glycoprotein
PIP	Paediatric Investigation Plan
PL	Package Leaflet

Abbreviation	Definition
PPND	Pre-/Postnatal Development Testing
PR	Partial Response
PSP	Pediatric Study Plan
PV	Pharmacovigilance
QD	Once Daily
QTc	corrected QT interval
RE	Response Evaluable
RMM	Risk Minimisation Measure
RMP	Risk Management Plan
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SPM	Second Primary Malignancies
ULN	Upper Limit of Normal
US	United States

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 ALK POSITIVE NSCLC

- Incidence:

The worldwide age-standardized incidence of trachea, bronchus and lung cancer in 2022 was 23.6 per 100,000 population (28.8 per 100,000 population in Europe and 31.9 per 100,000 population in the US)The incidence of lung cancer worldwide, as well as in the United States and Europe available from GLOBOCAN 2022 database and factsheets and WHO is presented in Table 2.

Table 2 Estimates of Trachea, Bronchus, and Lung Cancer Incidence, Mortality, and 5-year Prevalence in 2022: Worldwide, Europe and the United States

Country	Number: (Incidence in million)	Incidence per 100,000 (World age-standardized rate)	Number Mortality	Mortality per 100,000 (World age-standardized rate)	5-year Prevalence (Number)	5-year Prevalence proportion (per 100,000)
Worldwide	2,480,675	23.6	1,817,469	16.8	3,221,461	40.9
United States	226,033	31.9	127,653	16.6	288,303	86.1
Europe	484,554	28.8	375,784	21.4	610,169	81.6
Source: WHO GLOBOCAN 2022						

Approximately 80%–85% of lung cancers are a histological subtype collectively known as non-small cell lung cancer (NSCLC), which is mainly comprised of lung adenocarcinoma, lung squamous cell carcinoma, and large cell lung carcinoma (Cancer Facts and Figures 2022). Around 40% of NSCLC patients are diagnosed with early-stage disease (stage I–IIIA) (Waser N et al 2022, National Lung Cancer Audit 2021).

According to a cross-sectional epidemiological analysis utilizing data from the Surveillance, Epidemiology, and End Results (SEER)-18 program and the National Program of Cancer Registries (NPCR), the annual incidence of all stage NSCLC was found to be 40.3 per 100,000 individuals from 2010 to 2017 in the SEER-18 program, whereas it was reported as 43.8 per 100,000 individuals in the NPCR (Ganti et al, 2021). Using data from the SEER Explorer database, the 5-year (2016-2020) age-adjusted incidence (per 100,000 population) was 20.9 for all stage adenocarcinoma, 9.9 for all stage squamous cell carcinoma and 0.5 for large cell carcinoma for both sexes in the US (SEER 2023).

Approximately 4–5% of NSCLC cases have been shown to harbor an anaplastic lymphoma kinase (ALK) fusion gene (Tian HX, et al. 2017; Chen MF, et al. 2023, Barlesi F, et al. 2016). Historically, standardized biomarker testing was not routinely done for early-stage NSCLC, making it difficult to accurately assess the proportion of ALK positivity in early-stage NSCLC. However, based on available evidence, no significant difference has been reported on the ALK positivity rate between early stage and advanced stage NSCLC (Chen MF, et al. 2023.

- Prevalence:

The 5-year worldwide prevalence of trachea, bronchus and lung cancer in 2022 was 3,221,461 with 5-year prevalence proportion of 40.9 per 100,000 population for both sexes (GLOBOCAN 2022). In Europe, the 5-year prevalence proportion was 81.6 per 100,000 population, while in the United States, the 5-year prevalence proportion was 86.1 per 100,000 population (GLOBOCAN 20202. The prevalence of lung cancer worldwide, in the United States and Europe (available from GLOBOCAN 2022 database and fact sheets, WHO) is presented in Table 2.

According to a meta-analysis and systematic review of 62 studies including a total of 20,541 NSCLC patients, ALK rearrangements occurred in 1,178 (5.7%) of patients. The frequencies of ALK rearrangements in more common in never-smokers than smokers (Fan et al, 2014). A one-year nationwide program of the French Cooperative Thoracic Intergroup included 17,664 patients with advanced NSCLC between April 2012 and April 2013. Of the 8134 molecular analyses performed to describe the frequency ALK rearrangement, 388 (5%) were found to be ALK positive (Barlesi et al, 2016).

- Demographics:

The incidence of all stages (localized, regional and metastatic) NSCLC increases exponentially with advancing age, and it is slightly higher in males compared to females (SEER 2023). NSCLC is higher in non-Hispanic Black or White groups compared to Asian groups (SEER 2023). In the US, a study reported that the incidence (per 100,000 population) gap of NSCLC between Caucasians and African Americans has kept narrowing throughout the three decades (from 20.7 in 1983-1992 to 15.5 in 1993-2002 to 11.5 in 2003-2012) (Wang et al, 2017).

Patients with ALK-positive NSCLC tend to have specific clinical features, including never or light smoking history, younger age, NSCLC with adenocarcinoma histology, and propensity to develop brain metastases (~50−60% of patients over the course of their disease) (Zhang et al. 2015; Johung et al. 2016).

The median age of patients with ALK-positive NSCLC is 52 years, which is younger than ALK-negative NSCLC patients (Chia et al, 2014). The frequencies of ALK rearrangements ranged from 0% to 30.65% in males and from 2.63% to 37.04% in

female patients with NSCLC based on a systematic review of 50 publications (Fan et al, 2014).

A meta-analysis by ethnicity and histology of 68 studies did not show big differences of EML4-ALK translocation rate between western (Europe, North America, or Australia) (6.4%) and Asian (5.4%) patients with lung adenocarcinoma (Dearden S et al. 2013).

A retrospective real world data study, which included 19,895 eligible patients with advanced NSCLC (stage IIIB- IV) diagnosed January 2015 – May 2019, showed no difference in prevalence between White (2.4%) and Black and African American (2.2%) patients, whereas Asians had a higher prevalence (6.3%) (Allen et al 2021).

- The main existing treatment options:

Early-stage ALK-positive NSCLC

Surgical resection remains the single most consistent and successful option for cure for patients with lung cancer in the early stages, if the cancer is completely resectable.

Treatment with platinum-based chemotherapy (up to four cycles) leads to improved overall survival (OS) compared to resection alone and is currently the standard of care (SOC) for patients with completely resected Stage IB (tumor≥ 4cm)−IIIA NSCLC (AJCC Version 7) (Postmus et al. 2017).

Chemotherapy regimens used in the adjuvant and neoadjuvant settings involve platinum-based doublets, which are the same as standard of care drugs used in the metastatic setting. According to NCCN and ESMO guidelines, cisplatin is recommended as the preferred platinum agent and carboplatin is used when cisplatin cannot be tolerated, or comorbidities exist. Agents that have been combined with either cisplatin or carboplatin include taxanes, vinorelbine, gemcitabine, etoposide and pemetrexed (NCCN 2023).

Although the treatment landscape has rapidly evolved in recent years with the approval of cancer immunotherapy regimens (Felip et al. 2021, Forde et al. 2022, O'Brien et al. 2022), the role of immunotherapy in ALK-positive NSCLC remains unclear. ALK-positive patients have either been excluded from most trials or the enrolled ALK-positive patients in the immunotherapy trials were too few for a robust assessment on immunotherapy's function in ALK-positive early-stage NSCLC. Thus far, for patients with early-stage ALK-positive NSCLC, platinum-based adjuvant chemotherapy after surgical resection remains the standard treatment (Pisters K et al, 2022).

Locally advanced or metastatic ALK-positive NSCLC

Treatment with an ALK inhibitor is preferred as the initial therapy for patients with advanced ALK-positive NSCLC (Owen et al 2023, Table 3). The currently approved targeted treatments are presented below:

Table 3 Currently approved treatments for ALK–positive advanced NSCLC

Brand name	International non-proprietary name	Indication	Date of approval
Xalkori®	crizotinib	• 1L treatment of adults with ALK-positive advanced NSCLC • 2L treatment of adults with previously treated ALK-positive advanced NSCLC	EU 23 October 2012 (conditional approval) 11 November 2016 (full approval)
Zykadia®	ceritinib	• as monotherapy is indicated for the 1L treatment of adult patients with ALK-positive advanced NSCLC • as monotherapy is indicated as 2L treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib	EU 06 May 2015 (conditional approval of the 2L treatment) 23 June 2017 (approval of the 1L treatment)
Alunbrig®	brigatinib	• as monotherapy is indicated as 1L treatment of adult patients with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor • as monotherapy for the 2L treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib	EU 22 November 2018 (2L treatment) 01 April 2020 (1L treatment)

Brand name	International non-proprietary name	Indication	Date of approval
Lorviqua®	lorlatinib	• as monotherapy is indicated for the 1L treatment of adult patients with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor. • as monotherapy is indicated as 2L treatment of adult patients with ALK-positive advanced NSCLC whose disease has progressed after: ○ alectinib or ceritinib as the first ALK TKI therapy; or ○ crizotinib and at least one other ALK TKI.	EU 06 May 2019 (conditional approval of the 2L treatment) 27 Jan 2022 (extension of indication to 1L treatment)

1L = first line, 2L = second line, ALK = Anaplastic Lymphoma Kinase, NSCLC = non-small cell lung cancer, TKI = tyrosine kinase inhibitor.

Platinum-based chemotherapy doublets are recommended in the ESMO 2020 and NCCN 2023 guidelines as the later-line treatment options for patients who exhausted available ALK inhibitors. The combination of atezolizumab, bevacizumab, paclitaxel and carboplatin is also included in the ESMO 2020 guideline.

- Risk factors for the disease:

Traditionally, the predominant risk factors for lung cancer are smoking and environmental exposure to carcinogens (Molina et al. 2008, Cancer Facts and Figures 2022). However, risk factors for ALK-positive NSCLC are not well understood – a greater proportion of this population have no smoking history, are female, and tend to present at a younger age than in the general lung cancer population, and changes to the ALK oncogene is a risk factor for lung cancer.

- Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Mortality and Morbidity: NSCLC is associated with poor survival even when the diagnosis is made at an early stage due to a high risk of micrometastasis. The lung cancer death rate has declined by 56% since 1990 in men and by 32% since 2002 in women due to reductions in smoking, with the pace accelerating in recent years. From 2008 to 2017; the rate decreased by about 5% per year in men and 4% per year in women (Cancer Facts and Figures 2022). The overall 5-year relative survival rate for lung and bronchus cancer (2013-2019) was estimated to be 25.4%, while the survival was 62.8% for localized stage, 34.8% for regional and 8.2% for distant or metastatic

stage. The 5-year relative survival for all stages adenocarcinoma was 32.2%, squamous cell was 24.2% and large cell carcinoma was 21.4% (SEER 2023).

There are varying opinions on the implications of ALK positivity for survival, with most concluding ALK-positivity is a poor prognostic factor in NSCLC (Chia et al, 2014). In a prospective analysis of 116 lung cancer patients (of which 14.6% were ALK-positive upon screening), the median overall survival was not reached for ALK-positive patients (94.1% of ALK-positive patients received crizotinib), therefore being significantly longer than for ALK-negative patients (HR for death =2.98, 95% CI =1.29–6.90, P=0.01).

Studies on the prognostic impact of ALK in early-stage disease have generated variable outcomes (Yang et al. 2012, Blackhall et al. 2014, Boros et al. 2017, Shi et al. 2020). Establishing the true prognostic impact of ALK status in early-stage lung cancer can be challenging, and potential confounders have to be taken into account.

- Pregnancy Outcomes in ALK-positive NSCLC Patients

Lung cancer during pregnancy remains a rather uncommon condition with less than 70 cases published until 2016. Non-small cell lung carcinoma is the commonest type accounting for about 85% of all cases (mainly adenocarcinoma). Overall survival rates are low, with most patients dying within one year. Chemotherapy and/or targeted treatment have been used with poor outcomes. The disease has been also found to affect the products of conception (placenta and fetus) with no short- or long-term consequences for the neonate (Mitrou 2016).

A retrospective analysis of patients, conducted between 2009 and 2015, identified 2422 women with NSCLC, with 160 in the reproductive age. Among them, there were eight (5%) pregnant women diagnosed with Stage IV NSCLC (6 were treated with crizotinib and two patients were treated with gefitinib and erlotinib, respectively). Six out of these eight cases were ALK positive. Pregnancy termination occurred in two (25%) of the eight women. Placental abruption and premature delivery due to cervical incompetence occurred in two (25%) patients. The remaining patients delivered healthy babies. The postpartum maternal outcome was very poor, the median overall survival not exceeding 30 months for all the cases (Dagogo-Jack 2017).

A retrospective pooled analysis of 77 patients diagnosed with gestational lung cancer (ALK mutation in 47%) were identified in China from 2008 to 2019. A total of 11 cases of pregnancy-associated NSCLC were identified, of which four were ALK positive. Of the four ALK-positive patients, the fetal outcome was known in three (one live birth and two induced abortions). Three of four patients with ALK rearrangements received targeted therapies and were alive at the time of the analysis, while one patient died after 16 months of NSCLC diagnosis (Yang et al, 2021).

An analysis of a French prospective database and systematic review (2009 -2021) identified 11 pregnant women diagnosed with NSCLC (four metastastatic), of which five

patients were ALK-positive and six were EGFR-positive. Two patients were treated with crizotinib. In 10 (90.9%) of the 11 patients, premature delivery was induced, and anamnios occurred in one patient treated by osimertinib and trastuzumab. While no newborn malformations were observed, five newborns were hypotrophic. No developmental anomalies were found in the newborns. Caesarean sections were opted for all the pregnancies. No adverse fetal anomalies were observed (one newborn was found to be having hexadactyly). Intrauterine growth retardation was observed in three patients (28%). Post-partum maternal outcome was adverse in 2 patients with fatal outcomes after 3 days and 30 days respectively (Boudy 2021).

- Important co-morbidities:

In a retrospective study, Belot et al. reported that the most prevalent comorbidities in metastatic NSCLC are chronic obstructive pulmonary disease (COPD) (21.5%), myocardial infarction (5.4%), peripheral vascular disease (6.4%), cerebrovascular disease (6.1%) and congestive heart failure (5.2%) (Belot et al, 2019). Another study in overall NSCLC patients (irrespective of stage) reported hypertension (41.6%), COPD (21.5%), ischemic heart disease (17.3%), myocardial infarction (9.3%), and peripheral vascular disease (8.3%) as most prevalent comorbidities (Lembicz et al, 2018). In 164 patients with ALK positive NSCLC, the common comorbidities found were hypertension (30.5%), fluid and electrolyte disorder (25.6%), COPD (23.2%), liver disease (12.8%), and diabetes (10.4%) (Dalal et al, 2018).

Table 4 summarizes the prevalence of most common comorbidities in NSCLC patients.

Table 4 Prevalence of most common comorbidities in NSCLC patients

Comorbid Conditions	Advanced stage NSCLC, England, mean age: 72.81±10.90 years [a]	ALK+ NSCLC, United States, Median age: 55 years [b]	All stage, Poland, mean age: 64±7.47 years [c]
Hypertension	N/A	30.5%	41.6%
COPD	21.5%	23.2%	21.5%
Fluid and electrolyte disorders	N/A	25.6%	N/A
Liver disease	N/A	12.8%	N/A
Ischemic heart disease	N/A	N/A	17.3%
Diabetes	N/A	10.4%	11.0%
Myocardial Infarction	5.4%	N/A	9.3%
Peripheral vascular disease	6.4%	5.5%	8.3%
Cerebrovascular disease	6.1%	N/A	N/A
Congestive heart failure	5.2%	10.4%	N/A

N/A= not available, COPD= chronic obstructive pulmonary disease.

[a] Source: Belot et al, 2019

[b] Source: Dalal et al, 2018

[c] Source: Lembicz et al, 2018

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical safety studies and relevance to human usage:

Repeat-dose Toxicity:

Findings observed in Good Laboratory Practice (GLP) repeat-dose toxicity studies were generally minimal to mild. Changes observed in GLP studies either resolved or showed a tendency to resolve after a 4- or 8-week recovery period (in 4- and 13-week studies, respectively).

The main findings in both rats and monkeys at or slightly above clinically relevant exposures in the GLP studies were:

- effects on the erythroid system (abnormal red blood cell morphology [poikilocytosis], and mild anemia or changes in response to anemia)
- gastrointestinal (GI) findings (proliferative zone extension in GI mucosa in both species; in rats, degeneration of glandular epithelium of stomach, and

macrophages/multinucleated giant cell/inflammatory cell infiltration in GI mucosa and disarrangement/desquamation of small intestinal epithelium etc; and in monkeys, large intestine dilatation); effects on the GI tract were considered dose-limiting in monkeys

- hepatobiliary effects (increased hepatic alkaline phosphatase [ALP], direct bilirubin, γ-glutamyl transpeptidase and liver weight, vacuolation/degeneration/necrosis of bile duct epithelium, inflammatory cell infiltration in Glisson's sheath, enlargement/focal necrosis of hepatocytes, enlargement of Kupffer cells etc.)
- hypertrophy in the adrenal cortex.

In rats only, the following main changes were seen:

- effects on respiratory organs (increase in foamy macrophages in alveoli, macrophages/multinucleated giant cell/inflammatory cell infiltration in tracheal mucosa, and disarrangement of tracheal epithelium)
- ileal hemorrhage accompanied by prolongation of clotting time (13-week study only)
- effects on bone (increased bone ALP and inorganic phosphorus, increased activated osteoclasts, and decreased trabecular bone)
- effects on incisor teeth in rats (disarrangement/degeneration/necrosis of ameloblasts and dilatation of capillaries in the papillary/odontoblast layer; 13-week study only).

Discussion:

The non-clinical data from two animal species at clinically relevant exposures indicate that hepatobiliary laboratory test elevations, hematologic abnormalities on the erythroid system, and GI disorders may occur in patients receiving alectinib. Hepatotoxicity (drug-induced liver injury, ALT increased, AST increased, and bilirubin increased), anemia, and GI disorders (nausea, vomiting, constipation, and diarrhea) have also been observed in humans while on alectinib treatment in clinical studies and are captured as adverse reactions in the EU SmPC (Section 4.8) for alectinib and being monitored by routine pharmacovigilance activities. The risk of hepatotoxicity is also captured under the special warnings and precautions (Section 4.4) for use section of the EU SmPC.

A potential mechanism for the observed nonclinical hepatobiliary effects may be the inhibition of the bile salt export pump transporter by alectinib (IC50 = 0.912 μM); however, this cannot be definitely concluded.

Non-clinical findings that occurred in one species only and/or slightly above clinically relevant exposures, or that may be stress related responses in animals, were adrenal hypertrophy, effects on respiratory organs, ileal hemorrhage accompanied by prolongation of clotting time, and effects on teeth and bone. Apart from effects on respiratory organs, no identified or potential risks have been identified in the clinical trial data that are related to these non-clinical findings. The clinical respiratory adverse events (AEs) reported are expected for the patient population.

No chronic toxicity studies of 26 weeks in rat and 39 weeks in monkey have been conducted. The available clinical data provide the most relevant safety information for an assessment of alectinib's general toxicity profile.

Reproductive and Embryo-Fetal Developmental Toxicity:

Effects on male and female reproductive organs in mature animals were investigated in the oral repeat-dose toxicity studies in rats and monkeys and no treatment-related histopathological abnormalities were detected.

Pilot (GLP) embryo-fetal developmental studies were conducted in pregnant rats and rabbits (1055407; 1055408).

Alectinib (at doses of 0, 3, 9 and 27 mg/kg/day) was administered orally once daily to pregnant Wistar rats (6 dams/group) during organogenesis (from gestation days [GD] 7 to 17) (1055407). Caesarean sections were conducted on GD 20. No dams died or showed moribundity. The doses of 9 mg/kg/day and above were maternally toxic. At 9 mg/kg/day (GD 17: C_{max}: 2140 ng/mL and AUC_{0-24}: 40,600 ng•h/mL), decrease in body weight gain was observed in dams. In this group, a decrease in fetal weight, an increase in visceral anomaly ratio (dilation of ureter, thymic cord, small heart ventricle and thinning of ventricular wall) and an increase in retarded ossification (decreases in the number of sacral and caudal vertebrae) were also observed. At 27 mg/kg/day (GD 17: C_{max}, 3590 ng/mL; AUC_{0-24h}, 66,400 ng•h/mL), decreases in body weight and food consumption, as well as some necropsy findings including red focus of the mucosa in the glandular stomach, were observed in dams. Also, total litter loss was observed in all dams in this group. It was concluded that alectinib was toxic to the reproductive function of dams and embryo-fetal development in rats. The NOAEL in this study for maternal and fetal toxicity was 3 mg/kg/day (C_{max}, 827 ng/mL; AUC_{0-24h}, 13,900 ng • h/mL on GD 17), and 9 mg/kg/day for reproductive function in dams.

In New Zealand White rabbits, alectinib (at doses of 0, 3, 9, and 27 mg/kg/day) was administered orally once daily during organogenesis (from GD 6 to GD 18; 6 dams/group) (1055408).. Cesarean sections were conducted on GD 28. No dams died or showed moribundity. At ≥ 9 mg/kg/day, poikilocytosis was observed in dams. The dose of 27 mg/kg/day was toxic to the dam and embryo-fetus. In dams (C_{max} 2090 ng/mL and AUC_{0-24} 43,200 ng•h/mL on GD 18), decreases in food consumption and body weight as well as changes in hematology and blood chemistry parameters which are considered to be related to anemia, malnutrition as well as inflammation and/or stress were observed, but gross lesions were not observed at necropsy. In this group, abortion (1 dam), total litter loss (2 dams), high post-implantation loss rate, low fetal weight, low placental weight, and high frequency of skeletal variations were also observed. It was concluded that alectinib was toxic to the reproductive function of dams and embryo-fetal development in rabbits. The no observed adverse effect level (NOAEL) in this study was 3 mg/kg/day (GD 18: AUC_{0-24h}, 2950 ng•h/mL) for maternal

toxicity in dams, and 9 mg/kg/day (GD 18: $AUC_{0\text{-}24h}$, 6650 ng•h/mL) for reproductive function in dams and embryo-fetal development.

Although embryo-fetal toxicity occurred only at maternally toxic doses in rats and rabbits, it was concluded that alectinib is harmful to pregnancy in rats and rabbits at clinically relevant exposures.

No studies have been conducted to assess the impact of alectinib on milk production or its presence in breast milk.

Discussion:

Nonclinical testing on pre-/postnatal development (PPND) for alectinib has not been conducted and would not be warranted. Given the non-clinical data, alectinib may cause fetal harm when administered to a pregnant woman; therefore, embryo-fetal toxicity is included in the 'special warnings and precautions for use' section (Section 4.4) as well as in the 'fertility, pregnancy and lactation' section (Section 4.6) of the alectinib EU SmPC. Embryo-fetal toxicity is being monitored through routine pharmacovigilance activities.

It has been reported in literature that alectinib is excreted in human milk (Shang et al 2023). Considering the potential risk for the infant, mothers should be advised against breast-feeding while receiving alectinib. In view of the general and developmental toxicity profile of alectinib, this recommendation is unlikely to change. Therefore, a PPND study is not required for the purpose of detecting possible effects on the breastfed infant.

Genotoxicity:

In genotoxicity studies of alectinib, no mutagenic potential was observed, but an increase in polyploidy of Chinese hamster lung cells and an increase in centromere-positive micronuclei in rats and human lymphoblastoid TK6 cells were observed. The data suggest that the mechanism of micronucleus induction was abnormal chromosome segregation (aneugenicity) and not a direct effect on chromosomes. For this thresholded micronucleus induction, the no observed effect level was 200 mg/kg/day in rats (mean Cmax, 1850 ng/mL; mean AUC 0-24h, 36700 ng•h/mL).

Discussion:

Given the non-clinical genotoxicity data, alectinib at 600 mg twice daily (BID) does not present an undue genotoxic risk for patients. However, precautionary measures are in place based on the aneugenic effect of alectinib. This risk is managed through routine risk minimization measures and pharmacovigilance activities. Therefore, the SmPC mandates a contraception period for female patients of childbearing potential receiving alectinib.

Carcinogenicity:

No carcinogenicity studies were conducted with alectinib.

Discussion:

Carcinogenicity studies have not been performed to establish the carcinogenic potential of alectinib. Clinical data available for second primary malignancies (SPM) did not link alectinib to the risk of SPM. In addition, a weight of evidence assessment which includes alectinib's low potency for micronucleus induction, its lack of mutagenicity or clastogenicity and the available literature data, suggests there is no additional cancer risk in patients derived from the aneugenic potential of alectinib. In line with a regulatory request to commit to performing a carcinogenicity program in accordance with ICHS1B, to be reported post-approval, associated with the procedure (EMEA/H/C/004164/II/0047), a 6-month transgenic TgHras2 mouse study and a 2-year rat carcinogenicity study are planned.

Safety pharmacology:

In the safety pharmacology studies, no effects on central nervous system (CNS), GI motor function, or respiratory system were observed with alectinib up to 300 mg/kg (mean C_{max}: 1770 ng/mL) in rats.

Cardiovascular system

In an in vitro Human ether-à-go-go-related gene (hERG) assay, alectinib inhibited hERG current with an IC20 and an IC50 of 58 and 217 ng/mL, respectively. Based on alectinib's plasma protein binding ratio of $>$ 99%, these concentrations are approximately 8- to 30-fold the anticipated free clinical C_{max} of $\approx$7 ng/mL.

In an explorative telemetry study in monkeys, a mild hypotension (approximately 10 mmHg) was seen at 20 and 60 mg/kg (mean estimated C_{max}: 719 and 695 ng/mL, respectively) with no effects on ECG or heart rate.

In the GLP-compliant telemetry study in monkeys, no effects on ECG, blood pressure or body temperature were observed up to 15 mg/kg orally (PO) (mean C_{max}: 279 ng/mL).

In addition, to elucidate the mechanism of hypotension observed in monkeys, two in vitro studies were conducted. In the first study, alectinib caused dilation of a rat isolated aorta pre-constricted with potassium (IC20, 7.38 ng/mL; IC50, 81.1 ng/mL). Because the L-type Ca2+ channel in vascular smooth muscle cells is a critical contributor to vasoconstriction, this channel was presumed to be involved in the hypotensive effect of alectinib. Alectinib inhibited the current of the CaV1.2 L-type Ca2+ channel (IC20, 98 ng/mL; IC50, 222 ng/mL), approximately 14 and 30-fold, respectively, the anticipated free clinical C_{max} of $\approx$7 nm/mL. Therefore, the hypotensive effect of alectinib observed in monkeys may have been caused by vasodilatation induced by L-type Ca2+ channel inhibition.

Discussion:

No safety concerns were identified from the results for effects on the CNS, GI motor function, and respiratory system.

Based on the non-clinical data, alectinib may have the potential to cause hypotension. Data from the alectinib pivotal clinical trials showed slight on-treatment decreases in systolic and diastolic blood pressure (median decrease of 6 mmHg and 7 mmHg, respectively; pooled data from the Phase II parts of pivotal studies NP28761 and NP28673) in patients with ALK+ NSCLC. Data from the Phase III pivotal clinical trial, BO28984, were consistent with that of the Phase II trials. Hypotension is not considered an adverse drug reaction with alectinib treatment, since few events have been reported: orthostatic hypotension: n=2 (0.8%); hypotension: n=2 (0.8%) in the pooled Phase II studies NP28761 and NP28673; orthostatic hypotension: n=0; hypotension: n=3 (2.0%); syncope n=1 (0.7%) in Phase III study BO28984.

Pooled ECG data from the Phase II parts of pivotal studies NP28761 and NP28673 (including intensive ECGs as triplicates and central reading) showed no evidence that alectinib caused any clinically relevant QTcF prolongation or change in cardiac function, with the exception of a decrease in HR which was generally asymptomatic, and follow-up data from Study NP28673 suggested that this decrease was reversible. Data from the pivotal Phase III study BO28984 were consistent with these analyses. A small number of patients (approximately 8% in the pooled Phase II studies NP28761 and NP28673, 11% in Phase III study BO28984) reported cardiac AEs of bradycardia and/or sinus bradycardia, all of which were Grade 1/2 in severity. “Bradycardia is included in the special warnings and precautions for use section (Section 4.4) of the alectinib EU SmPC and is being monitored through routine pharmacovigilance activities.”

Other toxicity-related information or data:

Photosafety:

Alectinib absorbs light in wavelengths from approximately 200 to 400 nm. A non-GLP in vitro photosafety test was therefore conducted with a fibroblast cell line Balb/c 3T3 in order to estimate potential phototoxicity risk of alectinib (0, 0.02 – 50 µg/mL). Based on the classification criteria of the OECD (Organisation for Economic Co-operation and Development) test guideline, a photo irritation factor (PIF = IC_{50} [- irradiation]/IC_{50} [+irradiation]) above 5 was judged to be phototoxicity-positive. Since alectinib was positive in this test (PIF = 94.8), and quantitative whole-body autoradiography of rats revealed distribution radioactivity to the skin and uvea, a potential risk of phototoxicity was suggested.

Discussion:

The non-clinical data indicate that alectinib may have the potential to cause photosensitivity in patients. Given the absorption spectra of alectinib (below the visible light range) and the characteristics of the adult human eye to absorb visible light only, no undue risk for alectinib-mediated retinal phototoxicity exists.

Photosensitivity has been observed in patients receiving alectinib in clinical trials; the majority of AEs were mild and generally did not lead to dose reductions or interruptions.

Photosensitivity is included in the special warnings and precautions for use section (Section 4.4) of the alectinib EU SmPC and is being monitored through routine pharmacovigilance activities.

Mechanisms for drug interactions:

In vitro studies indicate that:

- Neither alectinib nor its major active metabolite M4, competitively inhibited CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 at clinically relevant concentrations
- Alectinib is a competitive CYP2C8 inhibitor with a Ki value of 1.98 μM;
- Alectinib and its major metabolite M4 are weak time-dependent CYP3A4 inhibitors;
- Alectinib and its major metabolite M4 are substrates of CYP3A4;
- Alectinib exhibits a weak induction potential (~2-fold) of CYP1A2, CYP2B6 and CYP3A4;
- Alectinib and its major metabolite M4 are inhibitors of P-glycoprotein (P-gp) (IC_{50} = 1.13 and 4.68 μM, respectively) and Breast Cancer Resistance Protein (BCRP) (IC_{50} = 0.103 and 2.64 μM, respectively);
- Aqueous solubility of alectinib in vitro is pH dependent.

Discussion:

Co-administration of multiple oral doses of 400 mg posaconazole BID (CYP3A inhibitor), with a single oral dose of 300 mg alectinib and co-administration of multiple oral doses of 600 mg rifampicin once daily (CYP3A inducer), with a single oral dose of 600 mg alectinib exhibited only a minor effect on combined exposure of alectinib and M4.

Co-administration of multiple oral doses of 40 mg esomeprazole once daily, a proton pump inhibitor, demonstrated no clinically relevant effect on the combined exposure of alectinib and M4.

Results from a clinical drug-drug interaction study in ALK-positive NSCLC patients demonstrated that multiple doses of 600 mg alectinib have no influence on the exposure of midazolam (2 mg), a sensitive cytochrome P450 3A (CYP3A) substrate.

Physiologically based pharmacokinetic modeling supports that at clinically relevant concentrations alectinib is not expected to increase plasma concentrations of co-administered substrates of CYP2C8. Whereas, alectinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp or BCRP transporters; however, the increase in exposure is not expected to be more than 2-fold based on known published drug-drug interactions mediated through P-gp and BCRP transporters (Fenner et al. 2009; Schnepf and Zolk 2013).

Conclusion

No safety concerns from non-clinical data were considered as important identified risks or important potential risks.

Carcinogenicity is considered as missing information (SVII.3.2. Presentation of the Missing Information). Carcinogenicity studies (a 6-month transgenic TgHras2 mouse study and a 2-year rat carcinogenicity study) are listed as additional pharmacovigilance activities as described in Part III: Pharmacovigilance Plan (including post-authorisation safety studies).

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Exposure data presented in the tables below are derived from Studies NP28673, NP28761, AF-001JP, BO28984, and BO40336.

Exposure from the following studies have been pooled:

- NP28673 and NP28761 involving patients with ALK-positive advanced NSCLC previously treated with crizotinib
- BO28984 involving treatment-naïve ALK-positive NSCLC patients
- BO40336 involving adjuvant treatment of patients with completely resected Stage IB (tumors ≥4 cm) to stage IIIA ALK-positive NSCLC

Additionally, the tables below present the overall exposure in the metastatic population (studies BO28984, NP28673 and NP28761) separately from exposure in patients treated in the adjuvant setting (study BO40336).

For Studies NP28673 and NP28761, only patients receiving 600 mg twice daily (BID) have been included in the exposure tables below, with the exception of Table 6, which includes all patients receiving alectinib in studies NP28673 and NP28761 by dose.

Exposure data from Study AF-001JP, supporting the Japanese indication for alectinib 300 mg BID, is also presented separately. For this study, crizotinib-naïve patients with ALK-positive NSCLC receiving alectinib up to 300 mg BID (maximum dose provided in the study) have been included in the exposure tables.

EXPOSURE DATA FROM THE POOLED METASTATIC NSCLC (STUDIES NP28673, NP28761, BO28984) AND ADJUVANT NSCLC (STUDY BO40336) POPULATIONS

Table 5 Duration of Exposure

Duration of Exposure, Safety-Evaluable Patients
Protocol: BO28984, NP28673, NP28761 and BO40336

	Duration of exposure	Patients (N=533)	Person time*
Adjuvant	<= 3 months	7 (5.5%)	0.74
	> 3 - 6 months	4 (3.1%)	1.63
	> 6 - 12 months	1 (0.8%)	0.52
	> 12 - 18 months	4 (3.1%)	4.90
	> 18 months	112 (87.5%)	219.15
	Total patients numbers/person time	128 (100%)	226.95
Metastatic	<= 3 months	66 (16.3%)	8.20
	> 3 - 6 months	56 (13.8%)	20.64
	> 6 - 12 months	60 (14.8%)	43.61
	> 12 - 18 months	43 (10.6%)	53.56
	> 18 months	180 (44.4%)	625.04
	Total patients numbers/person time	405 (100%)	751.05
Overall	<= 3 months	73 (13.7%)	8.94
	> 3 - 6 months	60 (11.3%)	22.27
	> 6 - 12 months	61 (11.4%)	44.14
	> 12 - 18 months	47 (8.8%)	58.45
	> 18 months	292 (54.8%)	844.19
	Total patients numbers/person time	533 (100%)	978.00

Number of patients exposed to Alectinib.
* Person time is the sum of exposure across all patients in years.
Adjuvant includes study BO40336 and Metastatic includes studies BO28984, NP28673 and NP28761. Overall includes both Adjuvant and Metastatic studies.
Data cutoff: BO28984: 29NOV2019, NP28673: 27OCT2017, NP28761: 12OCT2017, BO40336: 26JUN2023.

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Table 6 Exposure by Dose

Extent of Exposure by Dose, Safety-Evaluable Patients
Protocol: BO28984, NP28673, NP28761 and BO40336

	Dose of Exposure	Patients (N=567)	Person time*
Adjuvant	Alectinib 600 mg	128 (100%)	226.95
	Total patients numbers/person time	128 (100%)	226.95
Metastatic	Alectinib 300 mg	7 (1.6%)	3.53
	Alectinib 460 mg	7 (1.6%)	12.94
	Alectinib 600 mg	405 (92.3%)	751.05
	Alectinib 760 mg	7 (1.6%)	15.84
	Alectinib 900 mg	13 (3.0%)	15.58
	Total patients numbers/person time	439 (100%)	798.93
Overall	Alectinib 300 mg	7 (1.2%)	3.53
	Alectinib 460 mg	7 (1.2%)	12.94
	Alectinib 600 mg	533 (94.0%)	978.00
	Alectinib 760 mg	7 (1.2%)	15.84
	Alectinib 900 mg	13 (2.3%)	15.58
	Total patients numbers/person time	567 (100%)	1025.88

Number of patients exposed to Alectinib.
* Person time is the sum of exposure across all patients in years.
Adjuvant includes study BO40336 and Metastatic includes studies BO28984, NP28673 and NP28761. Overall includes both Adjuvant and Metastatic studies.
Data cutoff: BO28984: 29NOV2019, NP28673: 27OCT2017, NP28761: 12OCT2017, BO40336: 26JUN2023.

Program: root/clinical_studies/RO5424802/share/pool_SCS_2023/prod/program/t_ex_bydose_rmp.sas
Output: root/clinical_studies/RO5424802/share/pool_SCS_2023/prod/output/t_ex_bydose_rmp_SE.out
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Table 7 Exposure by Age Group and Gender

Extent of Exposure by Age group and Gender, Safety-Evaluable Patients
Protocol: BO28984, NP28673, NP28761 and BO40336

		Patients			Person time*		
	Age group (years)	Male	Female	Total	Male	Female	Total
Adjuvant	18-40	15 (11.7%)	9 (7.0%)	24 (18.8%)	26.89	17.69	44.58
	41-64	28 (21.9%)	49 (38.3%)	77 (60.2%)	50.76	92.10	142.86
	>=65	11 (8.6%)	16 (12.5%)	27 (21.1%)	16.71	22.80	39.51
	Total patients numbers/person time	54 (42.2%)	74 (57.8%)	128 (100%)	94.35	132.59	226.95
Metastatic	18-40	18 (4.4%)	35 (8.6%)	53 (13.1%)	32.90	63.96	96.87
	41-64	135 (33.3%)	144 (35.6%)	279 (68.9%)	219.89	294.23	514.12
	>=65	30 (7.4%)	43 (10.6%)	73 (18.0%)	56.38	83.68	140.06
	Total patients numbers/person time	183 (45.2%)	222 (54.8%)	405 (100%)	309.17	441.88	751.05
Overall	18-40	33 (6.2%)	44 (8.3%)	77 (14.4%)	59.79	81.66	141.45
	41-64	163 (30.6%)	193 (36.2%)	356 (66.8%)	270.65	386.33	656.98
	>=65	41 (7.7%)	59 (11.1%)	100 (18.8%)	73.08	106.49	179.57
	Total patients numbers/person time	237 (44.5%)	296 (55.5%)	533 (100%)	403.52	574.47	978.00

Number of patients exposed to Alectinib.
* Person time is the sum of exposure across all patients in years.
Adjuvant includes study BO40336 and Metastatic includes studies BO28984, NP28673 and NP28761. Overall includes both Adjuvant and Metastatic studies.
Data cutoff: BO28984: 29NOV2019, NP28673: 27OCT2017, NP28761: 12OCT2017, BO40336: 26JUN2023.

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Table 8 Exposure by Racial Origin

Extent of Exposure by Race, Safety-Evaluable Patients
Protocol: BO28984, NP28673, NP28761 and BO40336

	Race	Patients (N=533)	Person time*
Adjuvant	Asian	70 (54.7%)	127.89
	Black or African American	1 (0.8%)	2.07
	White	55 (43.0%)	93.00
	Unknown	2 (1.6%)	3.99
	Total patients numbers/person time	128 (100%)	226.95
Metastatic	American Indian or Alaska Native	5 (1.2%)	11.15
	Asian	115 (28.4%)	237.07
	Black or African American	4 (1.0%)	5.25
	Native Hawaiian or other Pacific Islander	1 (0.2%)	4.68
	White	262 (64.7%)	470.82
	Other	11 (2.7%)	17.93
	Multiple	1 (0.2%)	0.19
	Unknown	6 (1.5%)	3.97
	Total patients numbers/person time	405 (100%)	751.05
Overall	American Indian or Alaska Native	5 (0.9%)	11.15
	Asian	185 (34.7%)	364.95
	Black or African American	5 (0.9%)	7.32
	Native Hawaiian or other Pacific Islander	1 (0.2%)	4.68
	White	317 (59.5%)	563.81
	Other	11 (2.1%)	17.93
	Multiple	1 (0.2%)	0.19
	Unknown	8 (1.5%)	7.96
	Total patients numbers/person time	533 (100%)	978.00

Number of patients exposed to Alectinib.
* Person time is the sum of exposure across all patients in years.
Adjuvant includes study BO40336 and Metastatic includes studies BO28984, NP28673 and NP28761. Overall includes both Adjuvant and Metastatic studies.
Data cutoff: BO28984: 29NOV2019, NP28673: 27OCT2017, NP28761: 12OCT2017, BO40336: 26JUN2023.

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Output: root/clinical_studies/RO5424802/share/pool_SCS_2023/prod/output/
t_ex_byrace_rmp_SE_GRRMP.out
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Table 9 Exposure by Ethnic Origin

Extent of Exposure by Ethnic Origin, Safety-Evaluable Patients
Protocol: BO28984, NP28673, NP28761 and BO40336

	Ethnicity	Patients (N=533)	Person time*
Adjuvant	Hispanic or Latino	1 (0.8%)	2.07
	Not Hispanic or Latino	125 (97.7%)	221.17
	Not Stated	2 (1.6%)	3.71
	Total patients numbers/person time	128 (100%)	226.95
Metastatic	Hispanic or Latino	30 (7.4%)	45.37
	Not Hispanic or Latino	369 (91.1%)	698.38
	Not Stated	6 (1.5%)	7.29
	Total patients numbers/person time	405 (100%)	751.05
Overall	Hispanic or Latino	31 (5.8%)	47.45
	Not Hispanic or Latino	494 (92.7%)	919.55
	Not Stated	8 (1.5%)	11.00
	Total patients numbers/person time	533 (100%)	978.00

Number of patients exposed to Alectinib.
* Person time is the sum of exposure across all patients in years.
Adjuvant includes study BO40336 and Metastatic includes studies BO28984, NP28673 and NP28761. Overall includes both Adjuvant and Metastatic studies.
Data cutoff: BO28984: 29NOV2019, NP28673: 27OCT2017, NP28761: 12OCT2017, BO40336: 26JUN2023.

Program: root/clinical_studies/RO5424802/share/pool_SCS_2023/prod/program/t_ex_byethnic_rmp.sas
Output: root/clinical_studies/RO5424802/share/pool_SCS_2023/prod/output/t_ex_byethnic_rmp_SE_GRRMP.out
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EXPOSURE DATA FROM STUDY AF-001JP

This study is conducted by Chugai Pharmaceuticals Co Ltd. in patients with NSCLC harboring the ALK fusion gene. All patients enrolled in Study AF-001JP were Asian (n=70). The data cutoff date for all exposure data from Study AF-001JP is 30 September 2015.

Table 10 Duration of Exposure

ppdur_OS1 Person and Person Years by Duration of Exposure
Protocol(s):AF001JP (IAF001JT)
Analysis:Safety Population

Duration of Exposure	Persons	Person Years
< 6 months	9	2.349
6 months -< 12 months	8	5.778
12 months -< 18 months	8	10.127
18 months -< 24 months	1	1.64
24 months -< 30 months	3	7.266
30 months -< 36 months	2	5.708
36 months -	39	185.845
Total	70	218.713

Program : $PROD/cdp70190/iaf001jo/ppdur.sas / Output : $PROD/cdp70190/iaf001jt/reports/ppdur_OS1.out
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Table 11 Exposure by Dose

ppdos_OS1 Person and Person Years by Dose of Exposure
Protocol(s):AF001JP (IAF001JT)
Analysis:Safety Population

Dose of Exposure (/day)	Persons	Person Years
40 mg	1	0.389
80 mg	1	0.914
160 mg	1	0.296
320 mg	3	12.698
480 mg	6	17.719
600 mg	58	186.697
Total	70	218.713

Program : $PROD/cdp70190/iaf001jo/ppdos.sas / Output : $PROD/cdp70190/iaf001jt/reports/ppdos_OS1.out
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Table 12 Exposure by Age Group and Gender

ppag_OS1 Person and Person Years by Age Group and Gender
Protocol(s):AF001JP (IAF001JT)
Analysis:Safety Population

	Persons		Person Years	
Age Group	Male	Female	Male	Female
< 18 years	–	–	–	–
18 - 65 years	31	33	88.285	113.407
> 65 years	2	4	10.393	6.628
Total	33	37	98.678	120.035

Program : $PROD/cdp70190/iaf001jo/ppag.sas / Output : $PROD/cdp70190/iaf001jt/reports/ppag_OS1.out

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PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Table 13 Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Hypersensitivity *Studies NP28673, NP28761, BO28984, and BO40336:* History of hypersensitivity to any of the excipients in the CH5424802 formulation (lactose monohydrate, crystalline cellulose, sodium starch glycolate, hydroxypropyl cellulose, sodium lauryl sulfate, and magnesium stearate).	Patients who are hypersensitive to these ingredients cannot take alectinib	No	Hypersensitivity is contraindicated in EU-SmPC.
Treatment with other ALK inhibitors *Studies NP28763 and NP28761:* Receipt of any other ALK inhibitors in addition to crizotinib.	To eliminate any possible confounding factors and allow suitable wash-out of previous therapies in order to adequately assess the efficacy and safety of alectinib.	No	This exclusion criterion was not related to the safety of the patient population.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Prior treatment / therapy *Studies NP28763 and NP28761:* Receipt of any prior cytotoxic chemotherapy for ALK positive NSCLC within 4 weeks prior to the first dose of study treatment. *Study BO28984:* Receipt of any prior systemic treatment for advanced or recurrent NSCLC (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC. *Study BO40336:* • Prior adjuvant radiotherapy for NSCLC. • Prior exposure to systemic anti-cancer therapy. • Prior exposure to an ALK inhibitor	To eliminate any possible confounding factors and allow suitable wash-out of previous therapies in order to adequately assess the efficacy and safety of alectinib.	No	This exclusion criterion was not related to the safety of the patient population.
Previous Malignancies *Studies NP28673, NP28761, BO28984 and BO40336:* Patients with a previous malignancy within the past 3 years (*Studies NP28673, NP28761, and BO28984*) / 5 years (study *BO40336*) other than curatively treated malignancies.	May interfere with, or for which the treatment might interfere with, the conduct of the study. The effects of alectinib have not been established on other malignancies. To properly assess the safety and efficacy of alectinib in a non-confounding manner, no recent history of other malignancies could be allowed.	No	This exclusion criterion was not related to the safety of the patient population.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Unresolved AEs/toxicities from previous treatment Grade ≥3 in Study NP28673 and Grade ≥2 in Study NP28761. Grade ≥3 in Study BO28984 (due to any prior therapy such as radiotherapy) - excluding alopecia - which have not shown improvement and are strictly considered to interfere with current study medication.	Any possible confounding conditions were excluded for the purposes of elucidating the safety and efficacy of alectinib.	No	This exclusion criterion was not related to the safety of the patient population.
Patients with potential pre-existing condition of QT prolongation *Studies NP28673, NP28761 and BO28984:* Patients with baseline QTc > 470 ms or patients with baseline symptomatic bradycardia < 45 beats per minute. Administration of agents with potential QT interval prolonging effects within 14 days prior to the first administration of study drug(s) and while on treatment.	The purpose of the trial was to assess the safety and efficacy of alectinib, including its effect on QT interval prolongation. In order to do this in a non-confounding manner, patients with a potential pre-existing condition of QT prolongation were excluded from the trial.	No	This exclusion criterion was not related to the safety of the patient population.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Concomitant strong/potent CYP3A inhibitors or inducers *Studies NP28673, NP28761 and BO28984:* Administration of strong/potent CYP3A inhibitors or inducers (except for oral corticosteroids up to 20 mg prednisolone equivalent per day in Studies NP28673 and NP28761) within 14 days prior to the first administration of study drug(s) and while on treatment. *Study BO40336:* Administration of strong/potent CYP450 3A inhibitors or inducers in Japanese patients participating in the serial/intensive PK sample collection within 14 days prior to the first dose of study treatment and while on treatment with alectinib up to Week 3.	Alectinib is known to be metabolized by CYP3A enzymes. The possibility of DDI with strong modulators of CYP3A activity could not be excluded at the time of initiating the alectinib clinical trials (Studies NP28673, NP28761, BO28984), which could have resulted in lower or higher than expected PK levels of alectinib potentially affecting its efficacy and safety profile.	No	This exclusion criterion was not related to the safety of the patient population.
Pregnancy and lactation *Studies NP28673, NP28761, BO28984, and BO40336:* Pregnant or lactating women.	This is a standard exclusion criterion for clinical trials across therapeutic indications due to the possibility of harm to the fetus. Moreover, ALK is known to be involved in embryonic CNS development, and its inhibition in non-clinical studies (rat and rabbit) has shown embryonic-fetal death, abortion, and visceral abnormalities.	No	It is highly unlikely that pregnant and lactating women receive this treatment (according to the label), therefore it is not relevant in clinical practice.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
HIV positive patients *Studies NP28673, NP28761, BO28984 and BO40336*: Known HIV positivity	Confounding factors such as current illness can impact the safety as well as the ability to understand the safety profile of alectinib.	No	This exclusion criterion was not related to the safety of the patient population.
Other significant concurrent disease/illness *Studies NP28673, NP28761, BO28984, and BO40336:* Any clinically significant concomitant disease or condition that could interfere with, or for which the treatment might interfere with, the conduct of the study or the absorption of oral medications or that would, in the opinion of the Principal Investigator, pose an unacceptable risk to the subject in this study.	Other significant concurrent diseases/illnesses could confound risk assessment.	No	This exclusion criterion was not related to the safety of the patient population.
Uncontrolled intercurrent illness or psychiatric illness/social situations *Studies NP28673 and NP28761*: Uncontrolled intercurrent illness or psychiatric illness/social situations that would limit compliance with study requirements. *Studies BO28984 and BO40336:* Any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol requirements and/or follow-up procedures should have been discussed with the patient before trial entry	Reason for exclusion was potential for non-compliance with study protocol.	No	This exclusion criterion was not related to the safety of the patient population.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Patients with severe renal impairment *Studies NP28673 and NP28761*: Serum creatinine > 2fold the Upper Limit of Normal [ULN] and calculated creatinine clearance of < 60 mL/min (Cockroft and Gault formula) *Study BO28984:* Estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease equation of < 45 mL/min/1.73 m^2 *Study BO40336*: Serum creatinine $\geq$ 1.5x ULN and creatinine clearance $\leq$ 60 ml/min	Confounding factors such as current illness can impact the safety as well as the ability to understand the safety profile of alectinib.	No	Data emerging during the conduct of the studies showed that Alectinib's systemic elimination is mainly via hepatic metabolism and subsequent excretion into the feces with negligible renal excretion and as such, safety profile in patients with severe renal impairment is expected to be similar to that of the overall patient population.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Patients with moderate or severe hepatic impairment *Studies NP28673 and NP28761*: ALT and AST > 2.5 fold the ULN (>5 fold ULN for patients with concurrent liver metastases) and bilirubin > 2 mg/dL *Study BO28984: Liver disease characterized by:* ALT or AST > 3 fold ULN (≥ 5 fold ULN for patients with concurrent liver metastasis) confirmed on two consecutive measurements *Study BO40336: Liver disease characterized by:* ALT or AST ≥ 3-fold ULN OR Impaired excretory function (e.g., hyperbilirubinemia) or synthetic function or other conditions of decompensated liver disease such as coagulopathy, hepatic encephalopathy, hypoalbuminemia, ascites, and bleeding from esophageal varices OR Acute viral (BO40336 active viral) or active autoimmune, alcoholic, or other types of acute hepatitis	Moderate or severe hepatic impairment could confound benefit-risk assessment.	No	Patients with moderate or severe hepatic impairment are potentially at risk of increased exposure of alectinib. A dedicated clinical study investigating the effect of hepatic impairment on the pharmacokinetics of alectinib (NP29783) has been completed (see Section SIV.3 for further details).

ALK = anaplastic lymphoma kinase; ALT = alanine amino transferase; AST = aspartate aminotransferase, CNS = central nervous system; CYP3A = cytochrome P450 3A; DDI = drug-drug interaction; eGFR = estimated Glomerular Filtration Rate; NSCLC = non-small cell lung cancer; PK = pharmacokinetics; SmPC = Summary of Product Characteristics; ULN = upper limit of normal.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical trial exposed population is thought to be representative of the population with ALK-positive NSCLC.

The non-clinical embryo-fetal developmental studies conducted in pregnant rats and rabbits have been described in the Non-Clinical Part II, Module SII.

No clinical studies in pregnant women have been conducted up to date. No non-interventional studies, including registries, were designed and conducted to obtain information in this population. Hence, the length of exposure in pregnant women cannot be currently estimated.

The SmPC for alectinib warrants that women of childbearing potential must be advised to avoid pregnancy while on treatment with alectinib. Moreover, no clinical studies of alectinib have been performed in pregnant women and based on its mechanism of action, alectinib may cause fetal harm when administered to a pregnant woman. Therefore, the SmPC mandates a contraception period for female patients of childbearing potential. Additionally, it has been reported in literature that alectinib is excreted in human breast milk (Shang et al.2023). Considering the potential harm to the infant, mothers are advised against breastfeeding during alectinib treatment.

Cumulative summary of pregnancy data presented in Annex 7. Overall, the review of these cases did not reveal any pattern or cluster of information related to the use of alectinib in pregnancy. Based on the available data, the MAH concludes that this risk is adequately described in the CDS and EU SmPC.

Table 14 Exposure of special populations included or not in clinical trial development program

Type of special population	Exposure
Pregnant women	Pregnant women were specific exclusion criteria in the alectinib clinical trial program.
Breastfeeding women	Not included in the clinical development program. Mothers are advised against breastfeeding during alectinib treatment

Type of special population	Exposure
Patients with relevant comorbidities	
Patients with hepatic impairment	An analysis performed on the pooled Phase II studies NP28761 and NP28673 revealed that 59 patients with mild hepatic impairment (total bilirubin less than or equal to upper limit of normal [ULN] and AST greater than ULN or total bilirubin > 1.0 to 1.5 times ULN and any AST) and 206 patients with normal hepatic function (total bilirubin less than or equal to ULN and AST less than or equal to ULN) were included. A dedicated clinical study investigating the effect of hepatic impairment on the pharmacokinetics of alectinib (NP29783) has been completed. In this study, 16 patients with hepatic impairment (8 subjects with moderate hepatic impairment and 8 subjects with severe hepatic impairment, as per Child-Pugh classification) and 12 matching healthy subjects were enrolled for a total of 28 subjects (see Table 15).
Patients with renal impairment	An analysis performed on the pooled Phase II studies NP28761 and NP28673 revealed that 141 patients with normal renal function (CrCL ≥ 90 mL/min), 104 patients with mild renal impairment (CrCL 60 to < 90 mL/min) and 21 with moderate renal impairment (CrCL 30 to < 60 mL/min) were included.
Patients with cardiovascular impairment	Not included in the clinical development program although there was no specific exclusion criteria in Study NP28673, BO28984 and BO40336. In Study NP28761, patients were excluded if they had history of myocardial infarction or stroke within 6 months, congestive heart failure greater than NYHA class II, unstable angina pectoris, cardiac arrhythmia requiring treatment or family history of sudden death from cardiac-related causes.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Patients were not excluded from the clinical development program based on ethnic origin.
Subpopulations carrying known and relevant genetic polymorphisms	Not included in the clinical development program

Type of special population	Exposure
Other	
Children	Currently not included in the clinical development program. ALK-positive NSCLC is not a disease associated with children aged < 18 years. A Paediatric Investigation Plan (PIP) waiver for the NSCLC indication was received from the European Medicines Agency (EMA) on 12 April 2013 and the Paediatric Study Plan (PSP) waiver was agreed by the FDA on 3 September 2014.
Elderly (aged ≥ 65 years)	Elderly patients were not excluded from the clinical trial program based on age alone (see Table 7, and Table 12).

AE = adverse event; AST = aspartate aminotransferase; CrCL = creatinine clearance; PIP = Paediatric Investigation Plan; PSP = Paediatric Study Plan; ULN = upper limit of normal.

Table 15 Subject Groups from Study NP29783

Cohort	Subject	Child-Pugh Class/Score	n
1	Healthy Control	Not applicable	12
2	Moderate Hepatic Impairment	B: 7 to 9	8
3	Severe Hepatic Impairment	C: 10 to 13	8

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 POST-AUTHORISATION EXPOSURE

SV.1.1 Method used to calculate exposure

Methodology

United States

The number of patients exposed to alectinib (Alecensa) was estimated based on milligrams of alectinib sold. The average milligrams per patient was calculated based on average treatment duration by segment and average daily dose taking dose reductions and compliance into account.

The split by line of therapy is estimated based on claims data and qualitative and quantitative market research projects.

The gender and age estimated percentages are based on the US Claims data.

Average daily dose

The recommended daily dose of alectinib in ALK-positive, metastatic NSCLC patients is 600 mg orally BID. The calculated actual average dose per day in ALK+ NSCLC is

estimated to be 1,171 mg per day, reflecting the fact that 94% of patients receive 600 mg BID as the starting dose (US Claims Data)

Dose assumptions are based on the U.S. claims data.

Duration of treatment (DOT)

The duration of therapy for first line (1L) and second line (2L) is informed by median progression-free survival rate in clinical trial data from U.S. and Global studies, persistence rate reported in US claims data, and true up to the actual product volume sales.

The third line (3L) duration of therapy is estimated to be 80% of the 2L duration.

It is estimated that the compliance rate is 85%.

Japan

Alectinib was first granted marketing approval in Japan under the brand name Alecensa on 4 July 2014, which is the international birth date (IBD) for this product. In Japan, Alecensa (alectinib) 300 mg BID is approved for ALK fusion gene-positive unresectable, recurrent or advanced NSCLC, and is marketed by Chugai Pharmaceutical Co., Ltd. The first approved dosage forms were 20 mg and 40 mg capsules, and these dosage forms were discontinued in April 2018. On 02 September 2015, a new dosage form, 150 mg capsules, was approved in Japan which is now used. Alecensa was approved in Japan on 21 February 2020 for ALK fusion–positive recurrent or refractory anaplastic large-cell lymphoma (ALCL). The recommended dose for ALCL is 300 mg BID (150 mg BID for patients who weigh less than 35 kg).

Alecensa was also approved in Taiwan on 21 December 2016, for the treatment of patients with ALK – positive, advanced NSCLC who have progressed on or are intolerant to crizotinib. The recommended dose is 600 mg BID and it is marketed by Chugai in 150 mg capsules to be taken orally. On 11 May 2018, Alecensa was approved for 1L treatment of patients with ALK-positive advanced NSCLC in Taiwan.

European Economic Area and Rest of World

The number of patients exposed to alectinib (Alecensa®) was estimated based on the kgs of alectinib sold. The volume sold by Roche is sourced from Roche supply chain and financial systems (Controlling Profitability Analysis [COPA]). The sales data are provided on a monthly basis; therefore, the exposure is available from the IBD to the nearest point to the DLP (i.e., 3 July 2023).

Table 16 Exposure to Alectinib in European Economic Area and Rest of World

Indication	DDD (in mg)	DOT (in months)	Average No. of Days in a Month	Patient Population (Incidence EU5)	Share	Compliance Factor	Split of Patients	Split of Volume
1L ALK+ NSCLC	1200	34.8	30.4	2665	70%	0.75	77%	90%
2L ALK+ NSCLC	1200	12.3	30.4	1856	30%	0.75	23%	10%

Note: The DOT for 1L is 41 months. However, since it has been in most of the market for only 24 months now, we have used 24 months for our calculation.

1L=first-line; 2L=second-line; ALK+=anaplastic lymphoma kinase positive; DDD=daily defined dose; DOT=duration of treatment; EU5=France, Germany, Italy, Spain, and United Kingdom; NSCLC=non-small cell lung cancer.

Post-Authorization Exposure

Cumulative Exposure from Marketing Experience

Since the IBD, an estimated cumulative total of 92,807 patients have received alectinib from marketing experience (Japan, n= 14,603; United States, n= 17,092; European Economic Area [EEA], n= 17,838; and Rest of World [RoW], n = 43,274).

Separate exposure tables for marketing experience are presented for the EEA, the United States and Japan (due to differences in the stratification of data in each region; see Annex 7).

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

On the basis of its pharmacological properties, the risk of abuse or misuse of alectinib is low.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Carcinogenicity has been included as missing information since this module of the RMP was last submitted. This change was made following a regulatory request to commit to performing a carcinogenicity program in accordance with ICHS1B, to be reported post-approval, associated with the procedure (EMEA/H/C/004164/II/0047).

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified risk:

There are no important identified risks for alectinib.

Information on important potential risks

There are no important potential risks for alectinib.

SVII.3.2. Presentation of the Missing Information

The only missing information safety concerns presented are those that have been selected to be part of the safety specification: i.e., those that are associated with additional pharmacovigilance or risk minimization activities.

Information on Missing Information

Carcinogenicity.

Evidence source:

The alectinib toxicology program was conducted under the ICH S9 framework for advanced cancer, and no carcinogenicity studies have been conducted to date with alectinib. This approach is supported by the assessment of the totality of nonclinical data (see Part II, Module SII) and clinical safety data with alectinib (DSR No 1119726).

Anticipated risk/consequence of the missing information

No concern has arisen in relation to second primary malignancies (SPMs) in the clinical use of alectinib. An exploratory analysis of SPMs following treatment with alectinib in the advanced ALK-positive NSCLC setting and the literature epidemiological data on SPM incidence in the NSCLC population was performed. In addition, data from the pivotal Phase III adjuvant trial BO40336 were included. The incidence of SPM in patients treated with alectinib was within the range of background incidence of SPM in the NSCLC population from epidemiological sources. No indication for an association between alectinib and the development of SPM could be identified from clinical safety data (DSR No: 1119726).

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 17 Summary of safety concerns

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

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

There are no ongoing routine PV activities beyond adverse reactions reporting, including specific pregnancy-related questions covered by the Global Pregnancy Reporting Form

for pregnancy cases occurring during alectinib treatment, and signal detection for alectinib.

The Roche standard pregnancy follow-up process was implemented for all products to request additional information on the medication history of the exposed parent, relevant medical history for the mother and father, previous obstetric history, the current pregnancy, fetal and infant conditions, and results of tests and investigations for any pregnancy complication or congenital abnormality during pregnancy or within the first year of the infant's life.

Cumulative data will be presented in PSURs/ PBRERs.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

The MAH plans to conduct two Category 3 non-clinical studies (a 6-month transgenic TgHras2 mouse study and a 2-year rat carcinogenicity study) in line with ICH S1B and in order to address missing information on carcinogenicity. These studies are summarized in Table 18.

III. 3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 18 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 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

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Table 19 Planned and Ongoing Post-Authorization Imposed Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies that are conditions of the marketing authorization				
ALINA (BO40336) (ongoing)	To evaluate the efficacy of alectinib compared with platinum-based chemotherapy in patients with completely resected Stage IB(tumors≥4cm) –Stage IIIA, ALK-positive NSCLC	Longer term efficacy (DFS and OS)	Submission of results of updated descriptive DFS and descriptive OS. Submission of results of 5-year survival follow up	Q3 2025 Q3 2027
Efficacy studies that are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				

DFS = disease-free survival; NSCLC = non-small cell lung cancer; OS = overall survival.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

V.1 ROUTINE RISK MINIMISATION MEASURES

Table 20 Description of Routine Risk-Minimization Measures by Safety Concern

Safety Concern	Routine Risk-Minimization Activities
Missing Information	
Carcinogenicity	**Routine risk communication:** None **Other risk minimization measures beyond the Product Information** None.

SmPC = Summary of Product Characteristics

V.2. ADDITIONAL RISK MINIMISATION MEASURES

None.

V.3 SUMMARY OF RISK MINIMISATION MEASURES

Table 21 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)

Q1 = first quarter; Q4 = fourth quarter

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PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR ALECTINIB (ALECENSA)

This is a summary of the risk management plan (RMP) for Alecensa. The RMP details important risks of Alecensa, how these risks can be minimized, and how more information will be obtained about Alecensa risks and uncertainties (missing information).

Alecensa summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Alecensa should be used.

This summary of the RMP for Alecensa should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Alecensa RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Adjuvant Treatment of Resected Non-Small Cell Lung Cancer
Alecensa as monotherapy is indicated as adjuvant treatment following complete tumour resection for adult patients with ALK-positive NSCLC at high risk of recurrence.

Treatment of Advanced Non-Small Cell Lung Cancer
Alecensa is authorized for the treatment (as monotherapy) of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib. Additionally, Alecensa as monotherapy is indicated for the first line treatment of adult patients with ALK-positive advanced NSCLC.

It contains alectinib as the active substance and it is given by oral administration.

Further information about the evaluation of Alecensa's benefits can be found in Alecensa's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Alecensa, together with measures to minimize such risks and the proposed studies for learning more about Alecensa risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A LIST OF IMPORTANT RISKS AND MISSING INFORMATION

Important risks of Alecensa are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Alecensa. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	Carcinogenicity

II.B SUMMARY OF IMPORTANT RISKS

There are no important risks for alectinib.

II.C POST-AUTHORISATION DEVELOPMENT PLAN

II.C.1 Studies which are conditions of the marketing authorization

Study BO40336 (ALINA) is a condition of the marketing authorization.

Study short name: Study BO40336 (ALINA)
Purpose of the study: To evaluate the efficacy of alectinib compared with platinum-based chemotherapy in patients with completely resected Stage IB (tumors≥4cm)–Stage IIIA, ALK-positive NSCLC.

II.C.2 Other studies in post-authorization development plan

Study short name:
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)

Purpose of the study:
To evaluate carcinogenic potential of alectinib in nonclinical carcinogenicity studies

Study short name:
Study 723267: 104-Week Rat Carcinogenicity Study (preliminary title; GLP study).

Purpose of the study:
To evaluate carcinogenic potential of alectinib in nonclinical carcinogenicity studies

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

There are no specific adverse event follow-up forms in use for this product.

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (if applicable)

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (if applicable)

Not applicable for this RMP.