12 October 2017
EMA/CHMP/833519/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Alecensa

International non-proprietary name: alectinib

Procedure No. EMEA/H/C/004164/II/0001

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

ADR adverse drug reaction

ALK anaplastic lymphoma kinase

ALT alanine aminotransferase

AST aspartate aminotransferase

BID twice daily

CI confidence interval

CL/F apparent plasma clearance

CNS central nervous system

CPK creatine phosphokinase

DOR duration of response

ECOG PS Eastern Cooperative Oncology Group Performance Status

eCRF electronic case report form

EML4-ALK echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase

ER exposure-response

FISH fluorescence in situ hybridization

GCP Good Clinical Practice

HR hazard ratio

IC50 50% of maximum inhibitory concentration

IDMC Independent Data Monitoring Committee

IHC kimmunohistochemistry

ILD: interstitial lung disease

IRF: Independent Review Facility

ITT: Intent-to-Treat

IxRS: interactive web response system

NCA: non-compartmental analysis

ORR: Objective response rate

OS: Overall survival

PK: pharmacokinetic

PFS: Progression free survival

PMDA: Pharmaceuticals and Medical Devices Agency

popPK: population pharmacokinetics

RT-PCR: reverse transcription polymerase chain reaction

TKI: tyrosine kinase inhibitor

TTR: Time to tumour response

V/F: volume of distribution

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration Limited submitted to the European Medicines Agency on 7 March 2017 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 and IIIB

Extension of Indication for Alecensa (alectinib) to first line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC); as a consequence, sections 4.1, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP are updated in accordance.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/1/2011 on the granting of a class waiver.

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 applicant 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.

Scientific advice

The applicant 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 Co-Rapporteur: Sinan B. Sarac

Timetable	Actual dates
Submission date	7 March 2017
Start of procedure	25 March 2017

Timetable	Actual dates
CHMP Rapporteur's preliminary assessment report circulated on	22 May 2017
CHMP Co- Rapporteur's preliminary assessment report circulated on	17 May 2017
PRAC Rapporteur's preliminary assessment report circulated on	25 May 2017
PRAC RMP advice and assessment overview adopted by PRAC	9 June 2017
Updated CHMP Rapporteur(s) (Joint) assessment report circulated on	16 June 2017
Request for supplementary information and extension of timetable adopted by the CHMP on	22 June 2017
MAH's responses submitted to the CHMP on	9 August 2017
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	13 September 2017
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	15 September 2017
PRAC RMP advice and assessment overview adopted by PRAC	28 September 2017
Joint Rapporteur's updated assessment report on the MAH's responses circulated on	6 October 2017
CHMP Opinion	12 October 2017

2. Scientific discussion

2.1. Introduction

NSCLC is the leading cause of cancer-related mortality worldwide and represents a major health problem. There are approximately 214,000 cases of NSCLC and 168,000 deaths per year in the United States (US), and 449,000 cases and 388,000 deaths per year in the European Union (EU) [GLOBOCAN 2012]. Survival rates for lung cancer tend to be much lower than for other common cancers, as a result of late diagnosis and limited effective therapies in advanced stages of the disease. The expected 5 year survival rate for all lung cancer patients in the US is only 18%, compared with 66% for colon cancer, 91% for breast cancer, and 99% for prostate cancer [Siegel et al 2016].

Approximately 5% of NSCLC cases have been shown to harbour the EML4 ALK fusion gene [Barlesi et al 2016] as a result of a chromosomal inversion at 2p21 and 2p23 [Choi et al 2010, Ou et al 2012]. The resulting ALK fusion protein results in activation and dysregulation of the gene's expression and signalling, which can contribute to increased cell proliferation and survival in tumours expressing these genes. Patients with 'ALK positive' tumours tend to have specific clinical features, including never or light smoking history, high frequencies in females, younger age, adenocarcinoma histology, and are sensitive to therapy with ALK inhibitors [Gridelli et al 2014]. ALK positive NSCLC patients can develop resistance and progression of disease particularly in the CNS resulting in poor prognosis.

Current First Line Treatment Options for ALK Positive NSCLC

Crizotinib is the current standard of care, and chemotherapy is also available as a first line treatment option for ALK positive NSCLC [ESMO guidelines 2016 and NCCN guidelines 2016]. Crizotinib and ceritinib are the only EU approved ALK inhibitors for the first line treatment of ALK positive NSCLC. The PROFILE 1014 study, a Phase III study of crizotinib compared with standard pemetrexed platinum based chemotherapy in previously untreated patients with ALK positive non squamous NSCLC

demonstrated a significant improvement in PFS (primary endpoint) with HR of 0.45 (95% confidence interval [CI]: [0.35, 0.60]; p < 0.001) and medians of 10.9 and 7.0 months for crizotinib and platinum based chemotherapy, respectively [Solomon BJ et al 2014]. The TT was significantly higher with crizotinib than with chemotherapy (74% [95% CI, 67 81] vs. 45% [95% CI, 37, 53], p < 0.001).

Although substantial benefit has been observed with crizotinib therapy, relapse remains the norm as on average patients progress within a year (median PFS = 10.9 months); survival after relapse is poor [Solomon B et al 2014]. The three main reasons for crizotinib treatment failure are: development of resistant mutations [Doebele et al 2012, Katayama et al 2011], activation of alternative pathways, e.g., epidermal growth factor receptor [Doebele et al 2012, Katayama et al 2011, Kim et al 2013] and CNS relapse [Costa et al 2011, Chun et al 2012, Weickhardt et al 2012]. The CNS is the primary site of progression in up to 46% of patients with ALK positive NSCLC treated with crizotinib [Costa et al 2011, Chun et al 2012, Weickhardt et al 2012]. Significant morbidity is associated with brain metastases as a function of brain involvement, and because of treatments required for disease control (corticosteroids, surgery, and radiation) [Roughley et al 2014, Owen et al 2014, Zimmermann et al 2014]. The presence of CNS metastases has also been shown to result in poor prognosis and shorter survival in patients with NSCLC [Sorensen et al 1988, Owen et al 2014, Zimmermann et al 2014].

In the first line setting, ceritinib also showed a statistically significant benefit over chemotherapy in delaying disease progression (PFS) with HR of 0.55 (95% CI: [0.42, 0.73]; p < 0.001) and medians of 16 months and 8 months respectively.

Alectinib (Alecensa) is a TKI that targets ALK and RET, thereby inhibiting intracellular signalling pathways involved in tumour cell proliferation and survival. Alectinib promotes cancer cell death by restoring apoptosis and inhibiting tumour cell growth and proliferation. Alectinib was first approved in Japan (2014) for treatment of ALK positive unresectable, recurrent or advanced NSCLC in patients who have progressed on or are intolerant to crizotinib (Xalkori).

In the EU, alectinib is approved for the treatment of ALK-positive advanced NSCLC previously treated with crizotinib since 16 February 2017.

The purpose of this application is to extend the indication of alectinib to include the first line treatment of patients with ALK-positive NSCLC. The MAH applied for the following change of indication which was adopted by the CHMP:

Alecensa as monotherapy is indicated for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

In the ERA submitted with the initial MAA, the maximum theoretical use of alectinib was refined based on the epidemiologically substantiated prevalence of ALK+ NSCLC. This means that the prevalence figure used comprises all expected cases of ALK+ NSCLC, not only the ones previously treated with crizotinib. Hence, the ERA as it stands covers the potential environmental risks deriving from all applications for ALK+ NSCLC. Therefore, no new or updated environmental risk assessment is needed for the current indication extension.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The applicant 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.

Table 1: Tabular overview of clinical studies in First-Line Treatment of NSCLC

Study Number	Objectives	Study Design	Patient Population	Dosing Regimen	Planned (Actual) Enrollment
BO28984 (ALEX) (Global, Roche-sponsored)	Efficacy, safety, tolerability, PK, patient reported outcomes	Phase III: randomized, active controlled, multicenter, open label	Patients who are treatment-naïve with advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) ALK-positive NSCLC and have ECOG PS of 0-2	Alectinib 600 mg BID orally or crizotinib 250 mg BID orally	286 (303 patients randomized); Study ongoing
JO28928 (J-ALEX) (Japan, Chugai-sponsored)	Efficacy, safety, tolerability, PK, patient reported outcomes	Phase III: randomized, active-controlled, multicenter, open-label	Patients who are ALK inhibitor-naïve and have received up to one line of chemotherapy for advanced ALK-positive NSCLC, and have ECOG PS of 0-2 and Stage IIIB not amenable to curative radiotherapy, IV or recurrent NSCLC	Alectinib 300 mg BID orally or crizotinib 250 mg BID orally	200 (207; 104 in crizotinib arm and 103 in alectinib arm); Data cutoff date: 03 December 2015
AF-001JP (Japan) First-in-human study	Safety, tolerability, efficacy, PK, investigation of food effect, effect on QT interval	Phase I: open-label, dose escalation phase Phase II: open-label cohort expansion phase evaluating safety and efficacy at the recommended dose determined in Phase I	Stage IIIB, IV or post-operative recurrent NSCLC, ALK inhibitor–naïve, ≥ 2 lines (Phase I) or ≥ 1 line (Phase II) of chemotherapy; and ECOG PS of 0 or 1	20, 40, 80, 160 mg (fasted) oral BID, 240 (fed/fasted), 300 mg (fed/fasted) oral BID	Phase I: 10-30 (24)[3] Phase II: 45 (46) Data cutoff date: 30 September 2015

ALK = anaplastic lymphoma kinase; BID = twice daily; ECOG PS = Eastern Cooperative Oncology Group Performance Status; NSCLC = non-small cell lung cancer; PK = pharmacokinetics.

[3] Twelve patients received alectinib 300 mg BID.

Source: J-ALEX CSR, AF-001JP CSR, and AF-001JP Updated Report

2.3.2. Pharmacokinetics

2.3.2.1. Methods

The clinical pharmacokinetic (PK) of alectinib was analysed by compartmental analysis using a popPK approach and in a limited subset of patients who underwent intensive PK assessment also by non-compartmental analysis (NCA). Descriptive statistics were used to summarize observed PK and NCA results.

Population pharmacokinetic PopPK analyses were conducted using pooled data from the two Phase III studies in ALK inhibitor-naïve patients, J ALEX and ALEX, along with data from the Phase I/II study, NP28673 to quantitatively describe the PK of alectinib and M4 in patients, and to evaluate the effects of relevant covariates (e.g., demographics, laboratory baseline values, disease status) that may contribute to the variability in alectinib and/or M4 exposure in individual patients.

The objectives of thePopPK analyses of the Phase III Studies J-ALEX and ALEX were to:

- Describe the PK of alectinib and its major active metabolite M4 in ALK-positive NSCLC patients who are ALK inhibitor-naïve,
- Confirm the effects of covariates which contribute significantly to the between-patient variability in PK parameters of alectinib and M4 in ALK inhibitor-naïve ALK-positive NSCLC patients,
- Determine individual estimates for derived secondary PK parameters for exposure-efficacy and -safety analyses and for summary statistics.

Following completion of the ALEX study, additional PK data was made available and all PK data from the ALEX study was analysed and reported separately (Study Report 1080486: Population Pharmacokinetic Analysis and Exposure-Efficacy and -Safety Analyses of Alectinib and M4 of Phase III Study BO28984 in ALK Inhibitor-Naïve Patients with ALK-Positive NSCLC).

The objectives of this analysis were the same as for the previous pooled PopPK analysis.

2.3.2.2. Data

In **J-ALEX**, PK samples were collected on Day 1 (baseline before dosing) and at steady-state on Day 57 and Day 113 at pre dose concentration at the end of a dosing interval (Ctrough). A total of 207 patients were randomized, of these 103 received alectinib and were included in the PK analysis.

In **ALEX**, a subset of patients (n = 10) randomized to receive alectinib underwent intensive PK sampling for determination of alectinib and M4 PK parameters by NCA methods. A total of six patients had PK samples collected up to 12 hours and four patients had PK samples collected up to 8 hours after the single dose (Visit 0; Baseline). Of these, nine patients had intense PK sampling available at steady-state (Visit 1; Week 4). A total of four patients had PK samples collected up to 12 hours and five patients had PK samples collected up to 8 hour post dose. Further, all patients randomized to receive alectinib treatment had sparse PK sampling taken pre-dose (C_{trough}; within 2 hours before intake of alectinib) at Visit 0 (Baseline before dosing), Visit 1 (Week 4), Visit 2 (Week 8) and at all subsequent visits (every 8 weeks) until progressive disease or death/withdrawal from the study. Based on QA'd plasma concentration data collected up to 28 June 2016, PK data were available from a total of 145 patients who were randomized to receive alectinib. At the clinical cut-off date of the 9th of February 2017, a total of 152 patients were randomized to the alectinib arm and were included in the second PopPK analysis.

A total of 1220 alectinib and 1220 M4 plasma concentrations measured from 228 ALK-positive ALK inhibitor-naïve NSCLC patients in J-ALEX and ALEX were available for the first, pooled, population PK analyses for each of these two entities. The final PK dataset used for the Bayesian feedback analyses consists of 986 alectinib and 978 M4 plasma concentrations collected from 228 patients in J-ALEX and ALEX. About 2.1% (21) and 3.0% (29) of the plasma concentrations for alectinib and M4, respectively, collected after start of treatment were BLQ and were excluded from the analysis dataset.

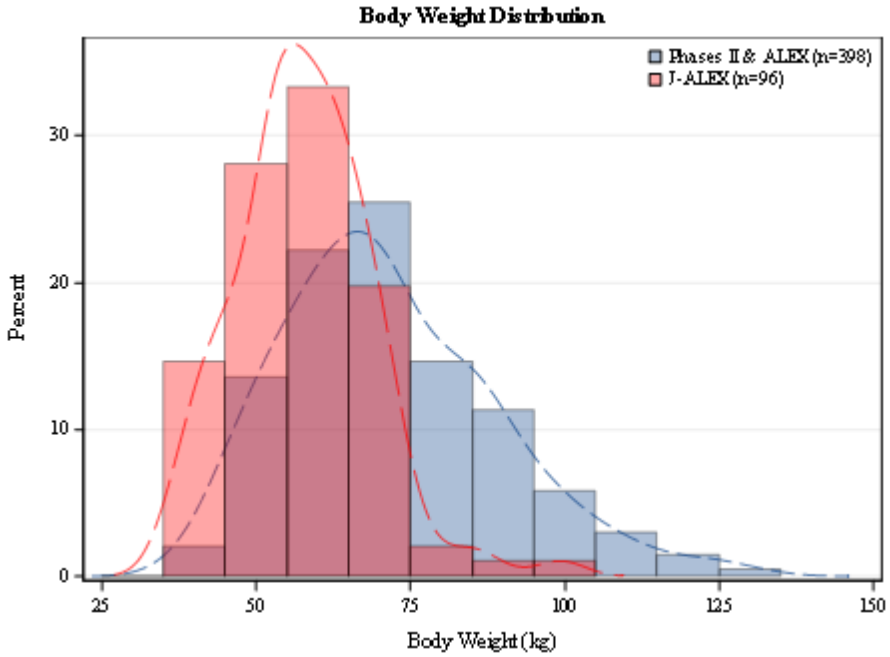
As for the second PopPK analysis using only ALEX data, A total of 1486 alectinib and 1486 M4 plasma concentrations measured from 143 ALK-positive ALK inhibitor-naïve NSCLC patients in ALEX were available for the population PK analyses for each of these two entities. Following data exclusions based o predefined criteria, the final PK dataset used for the Bayesian feedback analyses consists of 1302 alectinib and 1302 M4 plasma concentrations collected from 143 patients in ALEX.

2.3.2.3. Results

2.3.2.3.1. Demographics

The body weight of patients in the J-ALEX study was lower compared to ALEX and the previous Phase II population (see figure below). The median [range] body weight in was 56.9 kg [37.2 to 99.3] and 65 kg [40.4 to 131.5] in J-ALEX and ALEX, respectively. The patients' Body mass index (BMI) and body surface area (BSA) were also lower in J-ALEX compared to ALEX.

Figure 1 Body Weight Distribution for Patients in J-ALEX and ALEX and Phase II Studies



All patients in J-ALEX were Asian while 45% of the patients in ALEX were Asian and 50% of the patients were White. Approximately 60% of the patients were female in both J-ALEX and ALEX, and the distribution of age and baseline smoking status for patients in both studies were comparable. For the baseline laboratory values, patients in J-ALEX and ALEX are generally comparable, with the exception that patients in J-ALEX had higher baseline ALP compared to those in ALEX and patients in ALEX had higher baseline GGT compared to those in J-ALEX.

2.3.2.3.2. Summary statistics of observed PK and non-compartmental analysis

In the **J-ALEX** study, geo mean of individual median observed pre dose (Ctrough) concentrations across visits was 433 ng/mL for alectinib (geo mean CV%: 48.6) and 158 ng/mL (geo mean CV%: 45.4) for M4. The M4 to alectinib parent (M/P) ratio based on available data was approximately 40%.

Following administration of a single dose of 600 mg alectinib under fed conditions in the **ALEX** study, alectinib was absorbed with a median time to maximum concentration (Tmax) of 6.03 hours (range: 1.98 to 12.00 hours); the alectinib geometric mean maximum observed plasma concentration (Cmax) and area under the plasma concentration-time curve from time 0 to 8 hours (AUC0-8) were 211 ng/mL (geo mean CV%: 55.5%) and 713 ng•h/mL (geo mean CV%: 104.9%), respectively. The median Tmax for M4 was reached by 8.00 hours (range: 5.98 to 12.00 hours). The M4 geometric mean Cmax and AUC0-8 were 56.2 ng/mL (geo mean CV%: 80.1%) and 142 ng•h/mL (geo mean CV%: 191.7%), respectively.

Following BID administration in patients under fed conditions, alectinib and M4 plasma concentration-time profiles at Visit 1 (Week 4) were relatively flat with low Cmax/Ctrough ratio (geo mean Cmax/pre-dose Ctrough was 1.20 for alectinib and 1.18 for M4). The geo mean alectinib Cmax was 717 ng/mL (geo mean CV%: 46.8%) at a median Tmax of 4.02 hours post dose (range: 2.00 to 8.00) and AUC0-8 was 5030 ng•h/mL (geo mean CV%: 47.2%). The geo mean M4 Cmax was 321 ng/mL (geo mean CV%: 32.0%) at a median Tmax of 6.00 hours post dose (range: 2.00 to 10.00) and AUC0-8 was 2230 ng•h/mL (geo mean CV%: 37.0%).

2.3.2.3.3. Population pharmacokinetic analysis

Pooled PopPK analysis of J-ALEX and (partial) ALEX data

A Bayesian feedback analysis was conducted to analyze data from J-ALEX and ALEX utilizing the population PK models previously developed for alectinib and M4 in ALK positive NSCLC patients who have progressed on or intolerant to crizotinib (NONMEM version 7.2.0). For the Bayesian feedback analysis, the original models developed for alectinib and M4 were used by fixing the population parameters to their final values and by fixing to zero the number of maximal evaluation (i.e. MAXEVAL = 0) in the estimation subroutine (i.e ESTIMATION) in the NONMEM control streams. Bayesian feedback predictions (i.e. post-hoc) of individual PK parameters for alectinib and M4 were then derived from the individual observed concentration-time profiles. Goodness-of-fit plots as well as simulation based diagnostics (i.e. visual predictive checks [VPC]) were conducted to assess the performance of the previously developed popPK models in describing data for ALK positive NSCLC patients who were ALK inhibitor naïve.

The VPC's below show the median (solid red line), 95th and 5th percentiles (upper and lower dashed green lines) of observed concentrations and the corresponding prediction bands obtained from simulation of the model using the study design and individual covariates for study J-ALEX.

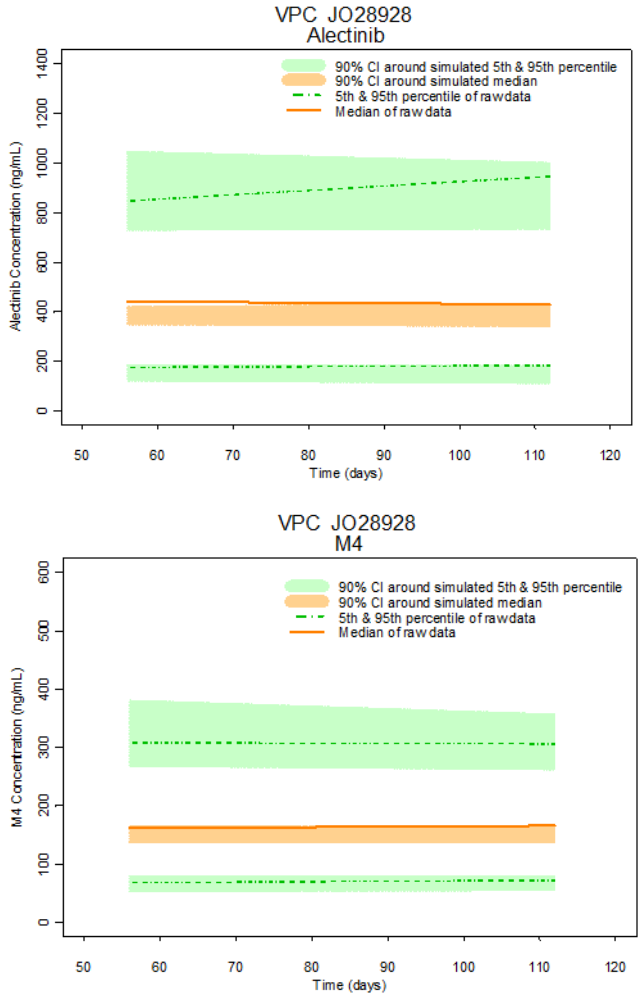


Figure 2: **Visual Predictive Check for Alectinib and M4 Concentrations from J-ALEX**

Pooled PopPK analysis of (final) ALEX data

The final PK dataset used for the PopPK analysis consisted of 1302 alectinib and 1302 M4 plasma concentrations collected from 143 patients in ALEX. Approximately 60% of the patients in ALEX were female, 48 % were white while 47% were Asian. Median (range) body weight was 65.2 kg (40.4 kg to 131.5 kg) and the median range age was 57 years (25 years to 81 years).

A Bayesian feedback analysis was conducted to analyze data from ALEX utilizing the population PK models previously developed for alectinib and M4 in ALK-positive NSCLC patients who have progressed on or intolerant to crizotinib. The adequacy of the model was assessed using VPC.

A one-compartment model with sequential zero and first order absorption could describe the data. Body weight was the only significant covariate for the PK of alectinib and M4, influencing the clearance (CL) and volume of distribution (V) according to allometric function with fixed exponents (0.75 for CL and 1.0 for V). The table below shows the influence of body weight on the predicted steady state exposure of alectinib following 600 mg bid dosing.

Table 2 Steady-State AUC12hr Derived for Alectinib and M4 Following 600 mg BID (Phase II Studies NP28673 & NP28761 and Phase III ALEX)

Population	Body Weight Category	n	$AUC_{ss,12hr}$ (ng × hr/mL) Geometric Mean (CV %)
Alectinib			
Phase II and ALEX 600 mg BID	BW < 60	109	9228 (33.0)
	60 ≤ BW < 90	241	7755 (40.2)
	BW ≥ 90	59	6094 (40.3)
M4			
Phase II and ALEX 600 mg BID	BW < 60	109	3890 (30.9)
	60 ≤ BW < 90	241	3055 (36.2)
	BW ≥ 90	59	2315 (41.2)

CV = coefficient of variation.

The VPC were updated using the entire ALEX PK dataset.

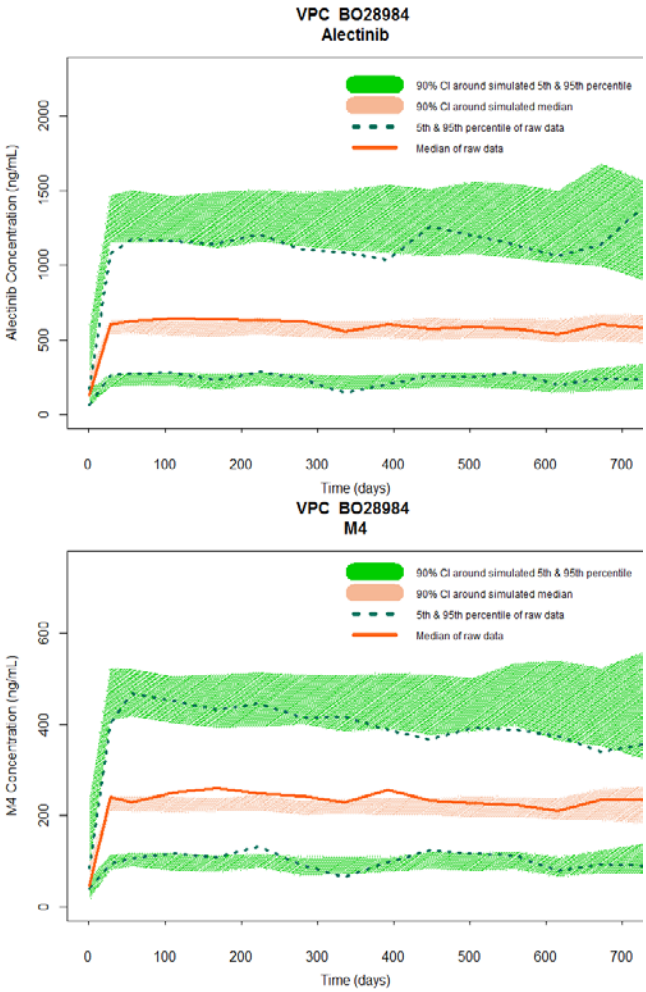


Figure 3: Visual Posterior Predictive Check for Alectinib and M4 – ALEX (BO28984)

2.3.3. Pharmacodynamics

Evaluations of PK/pharmacodynamics (PD) relationships for clinical efficacy from **J-ALEX** and selected clinical safety events from J-ALEX were conducted to quantitatively assess the ER relationship of alectinib in ALK inhibitor-naïve patients.

The objectives of the exposure-efficacy and -safety analyses of the Phase III Study J-ALEX were to:

- Investigate the exposure-efficacy and -safety relationship for alectinib and M4 in ALK-positive NSCLC patients who are ALK inhibitor-naïve at 300 mg BID,
- Determine whether the variability in efficacy and the occurrence of safety events could be attributed to the variability in alectinib and M4 exposure at 300 mg BID,
- Characterize the relationship between alectinib and M4 exposure and progression free survival (PFS) at 300 mg BID using a Cox proportional-hazards regression model.

Further, exposure-efficacy analyses were made using data from the **ALEX** study investigating whether the variability in PK exposure could explain part of the variability in efficacy at the dose of 600 mg BID in ALK-positive NSCLC patients who were ALK inhibitor-naive patients from ALEX who had PK data available were included in the exposure-response analyses.

2.3.3.1. Methods

Exposure-Efficacy

Individual Caverage, defined as the average concentration from first dose up to the time of efficacy (PFS) assessment derived from PopPK models, was used as the surrogate for exposure. Since M4 has been shown to have similar in vitro potency and exhibit similar protein binding as alectinib, the Caverage was defined as the average molar concentration of alectinib plus M4. Patients in the exposure-efficacy dataset were grouped into exposure categorizes based on their achieved Caverage.

The relationship between Caverage and efficacy was graphically investigated for the main efficacy parameter, PFS, by exposure categories and the log rank statistic was used to evaluate the graphical relationship.

A Cox proportional-hazards analysis was also conducted to characterize the relationship between Caverage and PFS. The two exposure categories were used in assessing exposure as a categorical parameter in the Cox proportional-hazards analysis. The analysis was conducted by accounting for the potential influence of additional factors such as baseline disease status covariates (e.g., tumor size, Eastern Cooperative Oncology Group score [0/1, 2], CNS metastases status [yes, no], prior chemotherapy [yes, no], prior crizotinib treatment duration), and demographic covariates (e.g., body weight, age, gender, race, ethnicity, smoking status [never, past/present]).

Using a forward inclusion followed by a backward deletion process, significant covariates for PFS were selected for the model. The Cox proportional hazards model which includes the statistically significant covariates is referred to as the final Cox proportional hazards model.

Exposure-Safety

Graphical analyses were performed to investigate whether the occurrence of safety events could be attributed to the variability in alectinib and M4 exposure at the 300 mg BID dose in ALK-positive NSCLC patients who were ALK inhibitor-naïve. Patients from J-ALEX who were included in the population PK analyses were included in these analyses.

2.3.3.2. Numbers analysed

The exposure-efficacy dataset for the analysis of J-ALEX comprised 96 patients while the analysis of ALEX included 143 patients.

2.3.3.3. Results

Exposure-Efficacy

For patients from J-ALEX treated with the 300 mg BID dose, results from the graphical analysis for PFS (see Figure 4 below) showed a positive ER relationship between alectinib exposure and PFS. Patients in both low and high alectinib exposure categories showed improved PFS over patients who were treated with crizotinib while patients in the high alectinib exposure category also appeared to have prolonged PFS compared to the low alectinib exposure category.

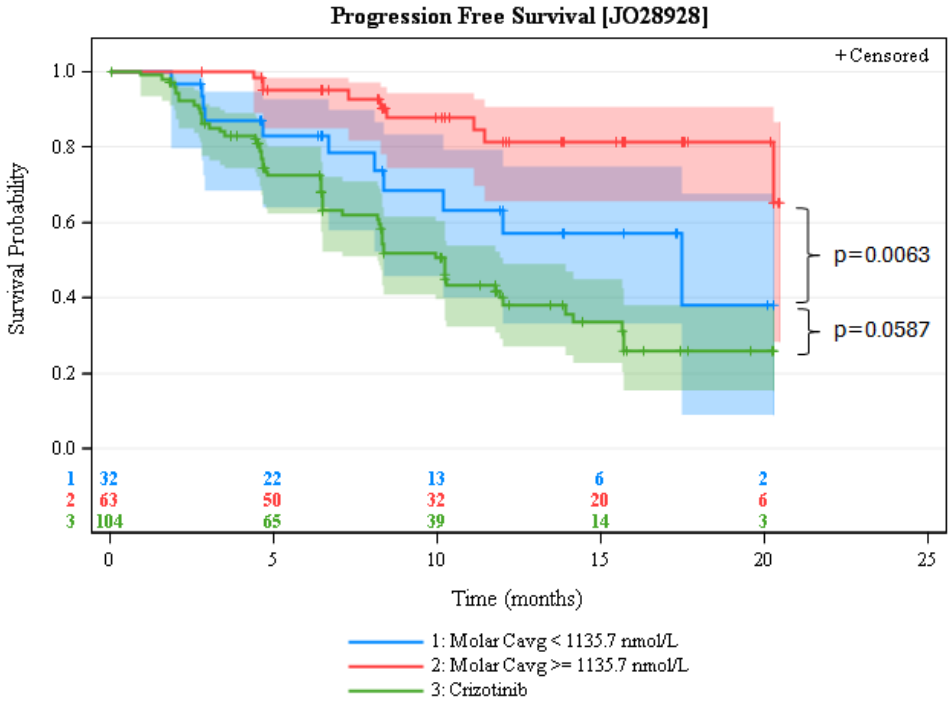


Figure 4 Study J-ALEX: Progression Free Survival versus Alectinib Low / High Exposure Groups Following Alectinib 300 mg BID and Crizotinib Treatment

For the primary efficacy endpoint of ALEX, PFS by investigator, patients in all exposure categories showed improved PFS compared to patients who were treated with crizotinib (Figure 5). However, the Kaplan-Meier plot showed that the relationship between Caverage and PFS by investigator was not significant (p=0.0911) across the 3 exposure categories.

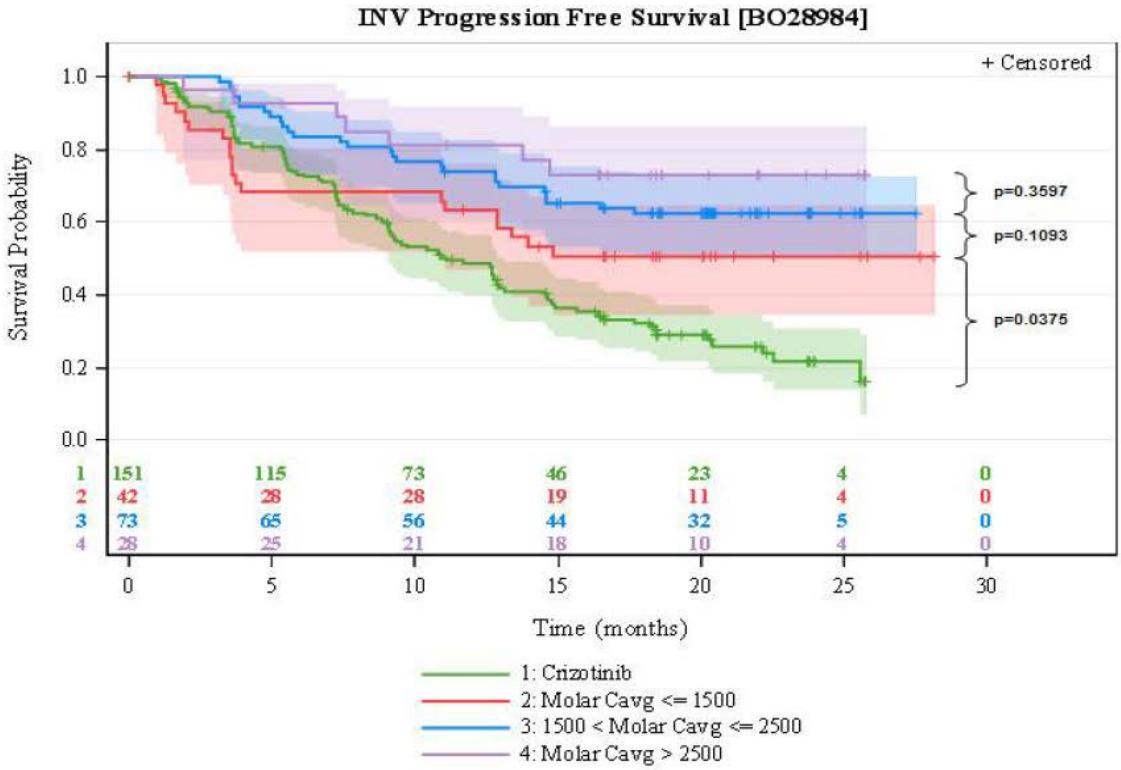


Figure 5 Study ALEX: Progression Free Survival (Investigator) by Exposure Category Following Alectinib 600 mg BID and Crizotinib Treatment

Results from the Cox proportional hazards analysis of J-ALEX demonstrated that alectinib exposure (i.e., the combined exposure of alectinib and M4) was the only covariate which was identified as a statistically significant predictor of PFS. The analysis showed that relative to crizotinib treatment, both alectinib low and high exposure categories are associated with an improved PFS with a larger magnitude of benefit associated with high alectinib exposure. Relative to crizotinib treatment, the HR for low and high alectinib exposures were 0.54 (95% CI: 0.28 to 1.02) and 0.17 (95% CI: 0.08 to 0.35), respectively.

Results of the Cox proportional-hazards analysis for PFS by investigator of the ALEX study showed that alectinib treatment effect, CNS metastasis at baseline, and baseline tumour size were the only statistically significant predictors of PFS.

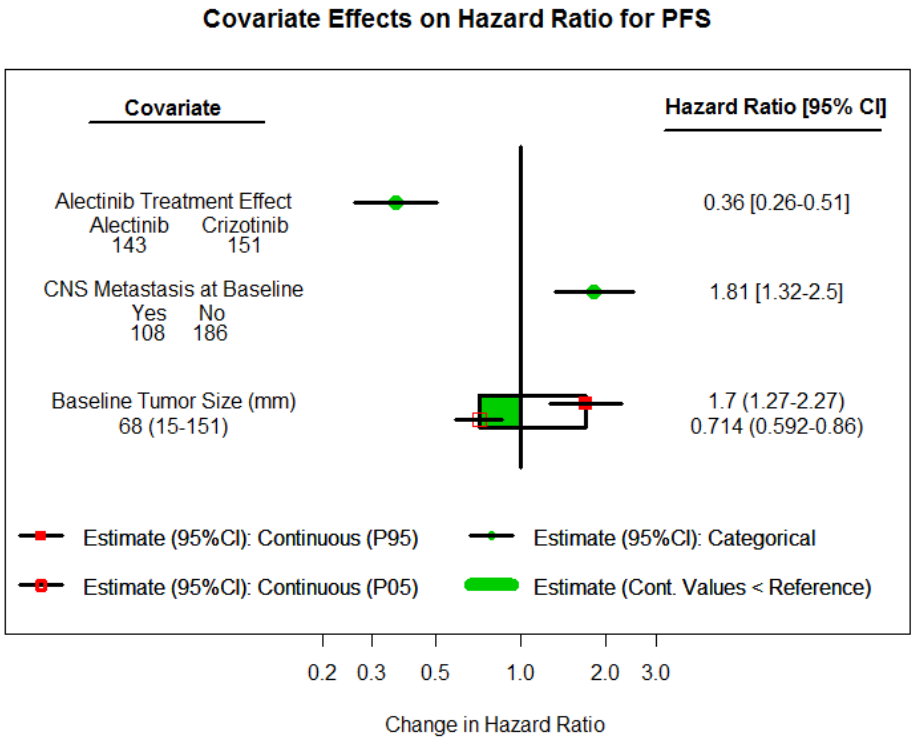


Figure 6: Covariate Effects of the Final Cox Proportional-Hazards Model for PFS by Investigator (ALEX)

Exposure-Safety

For patients receiving 300 mg BID in J-ALEX, logistic regression analyses have shown that there was no significant relationship between combined molar concentration of alectinib and M4 ($C_{average}$) and the occurrences of SAEs. There was also no significant relationship between $C_{average}$ and the occurrences of AEs Grade 3 or above. In addition, there was no apparent effect of $C_{average}$ on the severity of the first event for SAEs and AEs Grade 3 or above.

For patients receiving 600 mg BID in ALEX, logistic regression analyses showed that there was no significant relationship between combined molar concentration of alectinib and M4 ($C_{average}$) and the occurrences of SAEs. There was also no significant relationship between $C_{average}$ and the occurrences of AEs Grade 3 or above. In addition, there was no apparent effect of $C_{average}$ on the severity of the first event for SAEs and AEs Grade 3 or above.

2.3.4. Discussion on clinical pharmacology

The pharmacokinetics of alectinib and its major active metabolite (M4) have been characterised earlier in ALK-positive NSCLC patients and healthy subjects. In this application, additional information on the clinical pharmacology of alectinib was obtained by including results from two Phase III studies in ALK inhibitor naïve patients; JO28928 (J-ALEX) the BO28984 (ALEX) study. These data were analysed with population PK modelling along with data from the Phase I/II study, NP28673 to quantitatively describe the PK of alectinib and M4 in patients, and to evaluate the effects of relevant covariates (e.g., demographics, laboratory baseline values, disease status) that may contribute to the variability in alectinib and/or M4 exposure in individual patients.

Japanese patients in the J-ALEX study had lower body weight compared to patients in the ALEX study. This reflects the fact that the Japanese population on average has a lower body weight compared to a

western, white population. Since the dose in J ALEX (300 mg bid) was lower compared to ALEX (600 mg bid), the exposure is expected to be lower but not in proportion to dose since the lower body weight in J ALEX results in lower clearance and relatively higher exposure. Exposure to alectinib is related to body weight and with an identical dose the exposure is expected to be higher in a Japanese population compared to a western, white population. If Japanese patients were to be treated with 600 mg bid alectinib, relatively higher exposure is expected compared to a western, white population due to the difference in body weight.

Further, pharmacokinetic-pharmacodynamic modelling was applied to clinical efficacy as well as selected clinical safety events from J-ALEX and ALEX to quantitatively assess the exposure-response relationship of alectinib in ALK inhibitor-naïve patients.

The PK of alectinib in the ALK inhibitor naïve population from J-ALEX and ALEX was similar to the PK in patients who have progressed on or are intolerant to crizotinib. Essentially, the previously developed population PK model could reasonably well describe the PK data in the J-ALEX and ALEX study.

The exposure-efficacy analysis of J-ALEX indicated that the response in terms of PFS is related to alectinib and M4 exposure since patients with higher exposure seemed to have a lower risk of tumour progression. In the ALEX study there was no significant difference in the risk of progression when comparing groups with higher or lower exposure. However, the clinical pharmacology data provide support for the selected regimen.

2.3.5. Conclusions on clinical pharmacology

The pharmacokinetics of alectinib and its major metabolite M4 has been adequately characterized in ALK-positive NSCLC patients who are ALK inhibitor-naïve. Altogether the clinical pharmacology data provide support for the selected regimen.

2.4. Clinical efficacy

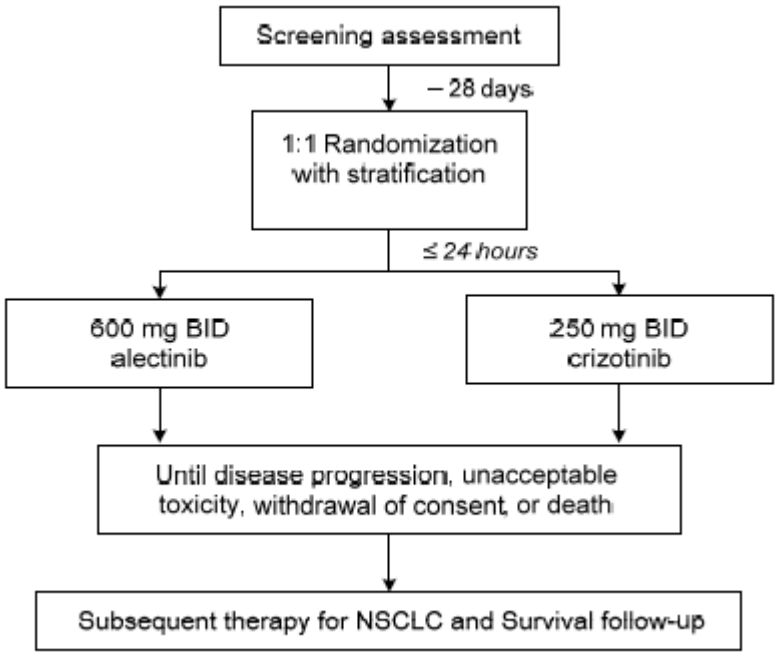
2.4.1. Dose response study

As opposed to the approved Japanese dose of alectinib i.e. 300 mg BID, the recommended global dose was set at 600 mg BID and reviewed in the initial application for licensure of alectinib (after failure on crizotinib [Xalkori] based on data from the single arm studies NP28761 and NP28673; EMEA/H/C/4164). The dose was determined primarily in the NP28761 study (Phase I dose escalation part) where a total of 47 patients with ALK positive NSCLC after failure on crizotinib, were enrolled and treated in cohorts in a staggered manner at an initial dose level of 600 mg/day. Study NP28673 also had a dose escalation portion (Part 1) but as the recommended phase II dose (RP2D) was considered established in study NP28761 further dose finding within NP28673 was not pursued.

2.4.2. Main study

Study BO28984 (ALEX): Randomized, Multicenter, Phase III, Open-Label Study of Alectinib versus Crizotinib in Treatment-Naive Anaplastic Lymphoma Kinase-Positive Advanced Non–Small Cell Lung Cancer.

Methods



BID = twice daily; n = number of patients; NSCLC = non-small cell lung cancer.

Study participants

Key inclusion Criteria

● Histological or cytological confirmed diagnosis of advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC that is ALK-positive as assessed by the Ventana IHC test. Sufficient tumour tissue to perform ALK IHC and ALK FISH was required. Both tests were performed at designated central laboratories.

● Age ≥ 18 years old

● Life expectancy of at least 12 weeks

● ECOG PS of 0-2

● No prior systemic treatment for advanced or recurrent NSCLC (Stage IIIB not amenable to multimodality treatment) or metastatic (Stage IV) NSCLC

● Adequate hematologic and renal function

● Measurable disease (by RECIST v1.1) prior to the administration of study treatment

● Prior brain or leptomeningeal metastases allowed if asymptomatic (e.g., diagnosed incidentally at study baseline). Asymptomatic CNS lesions might have been treated at the discretion of the investigator as per local clinical practice. If patients had neurological symptoms or signs due to CNS metastasis, patients needed to complete whole brain radiation or gamma knife irradiation treatment.

In all cases, radiation treatment must have been completed at least 14 days before enrolment and patients must have been clinically stable.

● Able and willing to provide written informed consent prior to performing any study-related procedures and to comply with the study protocol, including patients must have been willing and able to use the electronic patient-reported outcome (ePRO) device.

Key exclusion criteria

● Patients with a previous malignancy within the past 3 years were excluded (other than curatively treated basal cell carcinoma of the skin, early GI cancer by endoscopic resection, in situ carcinoma of the cervix, or any cured cancer that was considered to have no impact in PFS and OS for the current NSCLC).

● Any GI disorder that may have affected absorption of oral medications

● Liver disease characterized by: ALT or AST > 3 x ULN (≥ 5 x ULN for patients with concurrent liver metastasis) confirmed on two consecutive measurements

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 oesophageal varices

OR

Acute viral or active autoimmune, alcoholic, or other types of acute hepatitis

● NCI CTCAE (version 4.0) Grade 3 or higher toxicities due to any prior therapy such as radiotherapy (excluding alopecia), which had not shown improvement and were strictly considered to interfere with current study medication

● History of organ transplant

● Co-administration of anti-cancer therapies other than those administered in this study

● Patients with baseline QTc > 470 ms or symptomatic bradycardia

● Pregnant or lactating women

● Known HIV positivity or AIDS-related illness.

Treatments

Alectinib 600 mg was administered orally BID with food in the morning and evening. If a patient missed a dose, it could be taken within 6 hours of the scheduled time. If the time was greater than 6 hours, or if the patient vomited the dose, the patient was instructed to wait until the next scheduled time and take the next scheduled dose.

Crizotinib 250 mg was administered orally BID (with or without food) in the morning and evening. If a dose was missed, then it could be taken as soon as the patient remembered unless it was less than 6 hours until the next dose, in which case the patient was instructed to not take the missed dose. If vomiting occurred after taking a dose of crizotinib, the patient was instructed to take the next dose as scheduled.

Objectives

Primary efficacy objective

To evaluate and compare the efficacy of alectinib compared to crizotinib in patients with treatment-naive ALK-positive advanced NSCLC, as measured by investigator-assessed PFS.

Secondary efficacy objectives

● ORR and DOR

● Time to progression in the CNS on the basis of IRC review of radiographs by RECIST v1.1 and Revised Assessment in Neuro Oncology (RANO) criteria, as well as:

- To evaluate CNS objective response rate (C-ORR) in patients with CNS metastases who have measurable disease in the CNS at baseline.

- To assess CNS duration of response (C-DOR) in patients who have a CNS Objective Response.

- To assess CNS progression rates (C-PR) at 6, 12, 18, and 24 months on the basis of cumulative incidence.

● PFS assessment by the IRC

● OS

● Safety and tolerability of alectinib compared to crizotinib.

● PK characterization of alectinib and metabolite(s)

Outcomes / endpoints

Table 3: Summary of Efficacy Endpoints

Endpoint	Definition	Censoring
Primary		
PFS (investigator-assessed)	Time from date of randomization to the date of first documented disease progression or death, whichever occurs first	Last tumor assessment date for patients w/o PD or death (either during study treatment or during FU) at the time of analysis. Date of randomization for patients with no post-BL tumor assessment.
Secondary		
PFS (IRC-assessed)	Time from date of randomization to the date of first documented disease progression or death, whichever occurs first	Last tumor assessment date for patients w/o PD or death (either during study treatment or during FU) at the time of analysis. Date of randomization for patients with no post-BL tumor assessment.
Time to CNS progression (IRC-assessed)	Time from randomization until first radiographic evidence of CNS progression by independent review	Last tumor assessment date for patients w/o PD or death (either during study treatment or during FU) at the time of analysis. Date of randomization for patients with no post-BL tumor assessment
ORR (investigator-assessed)	Percentage of patients in the ITT population with measurable disease at baseline who attain a CR or PR	N/A
DOR	The duration from the first tumor assessment that supports the patient's objective response (CR or PR, whichever is first recorded) to first documented disease progression or death due to any cause, whichever occurred first	Last tumor assessment date for patients who have not progressed or died at the time of analysis
OS	Time from the date of randomization to the date of death due to any cause	Date when they were last known to be alive for patients who are not reported as having died at the time of analysis. Date of randomization for patients who do not have post-BL information.
CORR (IRC-assessed)	Proportion of patients achieving CR or PR of BL CNS lesions	N/A
CDOR (IRC-assessed)	Time from CNS response to CNS PD	Last tumor assessment date for patients who have not progressed or died at the time of analysis

BL = baseline; CDOR = CNS DOR; CNS = central nervous system; CORR = CNS ORR; CR = complete response; DOR = duration of response; FU = follow-up; IRC = independent review committee; ITT = intent-to-treat; N/A = not applicable; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; w/o = without.

The following endpoints were also considered:

- Time to deterioration (TTD) in patient-reported lung cancer symptoms of cough, dyspnoea (single item and multi-item subscales), chest pain, arm and shoulder pain, and fatigue as measured by the EORTC Quality of Life Questionnaire Core (QLQ-C30) and the supplemental lung cancer module (QLQ-LC13) as well as a composite of three symptoms (cough, dyspnoea, chest pain).

- PROs of health-related quality of life (HRQoL), patient functioning, and side effects of treatment as measured by the EORTC QLQ-C30 and EORTC QLQ-LC13.

Sample size

ALEX was designed to demonstrate superiority of alectinib versus crizotinib based on investigator-assessed PFS. The primary endpoint of PFS was used to determine the sample size of the study. A HR of 0.65 for alectinib versus crizotinib was targeted i.e. an increase in median PFS from 10.9 (based on the Phase III PROFILE 1014 study of crizotinib vs. standard pemetrexed-platinum-based chemotherapy) to 16.8 months. Approximately 170 PFS events were required to achieve 80% power of the log-rank test at a two-sided alpha level of 5%. A total of 286 patients were planned to be enrolled over approximately 24 months, and the required number of PFS events for the final PFS analysis was estimated to occur approximately 33 months after the first patient was enrolled.

Randomisation

Central randomization was performed and managed via an interactive voice or web-based response system (IxRS). Patients were randomized in a 1:1 allocation ratio to the two treatment arms via a block stratified randomization procedure.

Stratification factors

- ECOG PS (0/1 vs. 2),
- Race (Asian vs. non-Asian), and
- CNS metastases at baseline (yes vs. no).

Blinding (masking)

The study is open label.

Statistical methods

All tabulations of patient baseline characteristics and efficacy analyses were performed on the ITT population, defined as all randomized patients. Patients were assigned to their randomized treatment group.

The treatment comparison of PFS was based on a stratified log-rank test at the 5% level of significance (two-sided). For analysis purposes, stratification according to CNS metastases at baseline was performed on the basis of the IRC assessment rather than the investigator assessment. This was done because the independent assessment by neuroradiologists was deemed to be the most reliable and corresponded to the populations used to assess the CNS efficacy endpoints. The ECOG PS was not used for stratified analyses due to low patient numbers (7% in each arm with ECOG PS of 2), as pre-specified. Results from an unstratified log-rank test were prepared as a supportive analysis. Additional supportive analyses included Kaplan-Meier and Cox modeling approaches.

If the primary endpoint of investigator-assessed PFS was statistically significant at a two-sided 5% significance level based on the stratified log-rank test, the following secondary endpoints were tested in the following sequential order, each at a two-sided 5% significance level:

- PFS by IRC assessment
- Time to CNS progression by IRC RECIST
- ORR by investigator assessment
- OS

All tests in the sequence were based on a stratified log-rank test at the 5% level of significance (two-sided), with the exception of ORR in which a Mantel-Haenszel test was used. The stratification factors and the analysis population were the same as for the primary hypothesis test.

The primary endpoint, PFS, and other time-to-event endpoints was censored at last tumor assessment date for patients w/o PD or death (either during study treatment or during FU) at the time of analysis, or at date of randomization for patients with no post-baseline tumor assessment.

A sensitivity analysis was performed on the primary endpoint of investigator-assessed PFS to evaluate the robustness of the results. The sensitivity analysis included the following variations from the primary analysis:

- Censor patients at the last adequate tumor assessment prior to the start of non-protocol specified anti-cancer therapy received prior to observing progression.
- Censor patients for whom documentation of disease progression or death occurs after ≥2 missed tumor assessments. These patients were censored at the last tumor assessment prior to the missed assessments.
- Censor patients who discontinue study treatment (due to personal preference or toxicity) and/or withdraw or are lost to follow-up prior to observing disease progression.

Two additional sensitivity analyses for investigator-assessed PFS were performed:

- The effect of missing tumor assessments was evaluated if the number of missing assessments in either arm was > 5%. For patients with disease progression that was determined after one or more missing tumor assessments, the progression was backdated to the first missing tumor assessment.
- The effect of loss to follow-up was assessed if [redacted] % of patients were lost to follow-up for PFS in either treatment arm, a “worst-case” analysis was performed in which patients who were lost to follow-up were considered to have progressed at the last date they were known to be progression-free.

A sensitivity analysis for PFS and OS was also performed based on the stratification factors entered at randomization in the interactive web response system (IxRS) system.

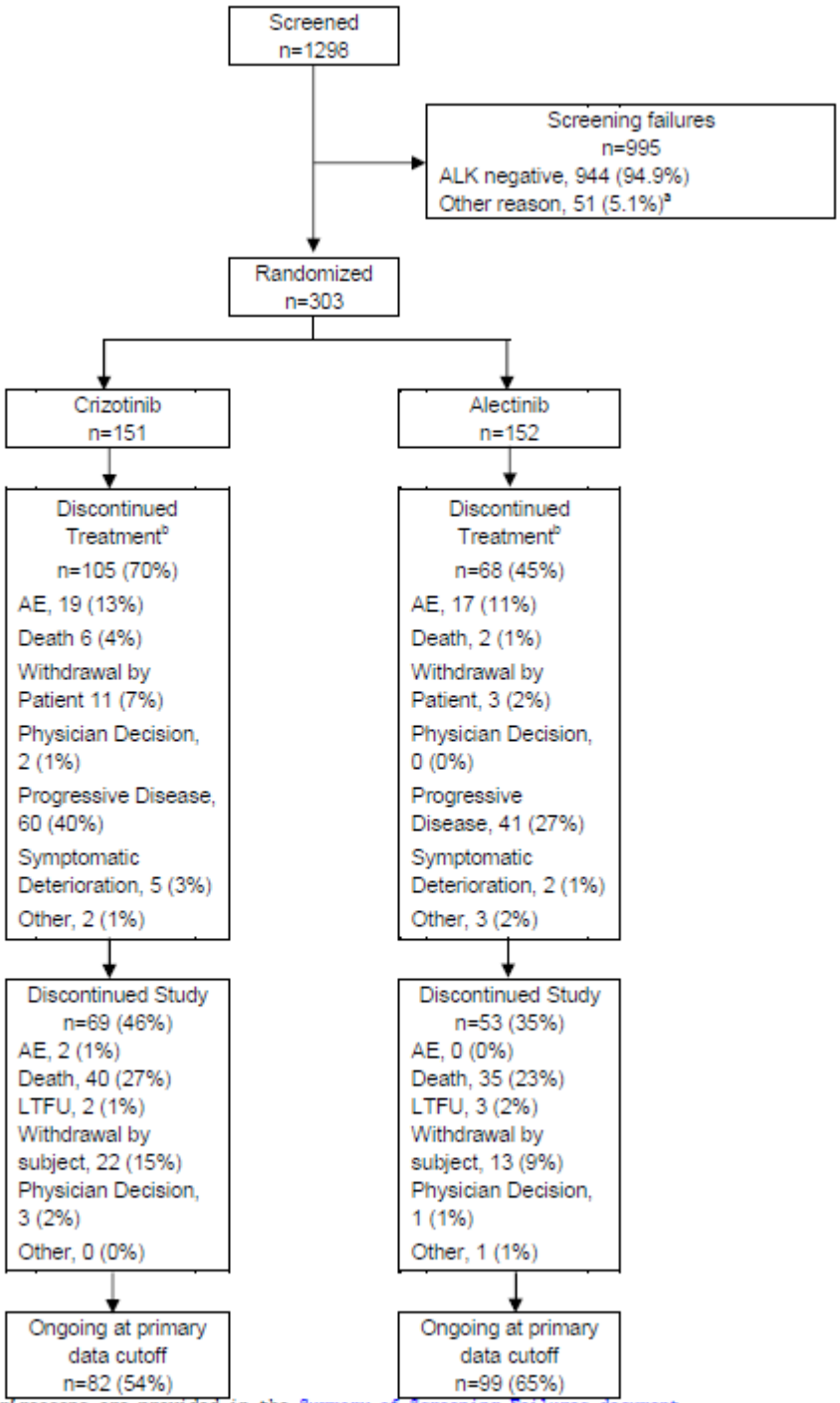
Subgroup analyses of investigator- and IRC-assessed PFS were conducted for the following:

- Age (<65 vs. ≥65)
- Sex (male vs. female)
- Race (Asian vs. non-Asian)
- Smoking status (active smoker vs. non-smoker vs. past smoker)

- Baseline prognostic characteristics: ECOG PS (0 vs. 1 vs. 2), CNS metastases at baseline as determined by IRC (yes vs. no), and prior brain radiation (yes vs. no)

Results

Participant flow



a Details of 'Other' reasons are provided in the Summary of Screening Failures document
b Patients who discontinued treatment were planned to be followed for safety and OS; these patients could remain in the study

Recruitment

Patients were recruited at 98 study sites in 29 countries. The first patient was enrolled on 19 August 2014 and the last patient was enrolled on 20 January 2016.

Conduct of the study

The initial protocol, dated 10 February 2014, was amended four times, including one local country amendment (Canada only).

Protocol Amendments

Protocol Amendment 1 (Version 2): 8 October 2014

Protocol Version 1 was amended to comply with questions addressed during the assessment of the Voluntary Harmonisation Procedure VHP444 (VHP201415), Western Institutional Review Board request (dated June 5, 2014) to further specify protocol inclusion criterion, FDA request (dated July 10, 2014) to revise crizotinib dose modification criteria for non-hematologic toxicities to conform to the most recent FDA approved label, as well as feedback from various other Health Authorities/Ethic Committees. Protocol BO28984 was amended to include the latest clinical and safety information. One main change was:

● Study rationale supplemented with latest crizotinib data from the recently published PROFILE 1014 study that lead to reassessment of assumptions for median PFS without impacting the target HR for the study. Protocol Amendment 2 (Version 3): 14 May 2015

Protocol Version 2 was amended to incorporate the latest pre-clinical and safety information. Changes include those to the specific timing of dose administration, pharmacokinetic objectives, concomitant therapy, and exploratory objectives.

Protocol Amendment 3 (Version 4): 15 April 2016

Protocol Version 3 was amended to incorporate the latest safety and alectinib administration information. Changes included those to AEs relating to alectinib data and management of alectinib AEs guidelines, restrictions related to QT-prolonging concomitant medications for alectinib, and guideline for the management of missing doses of alectinib.

A local amendment, Amendment 4 (Protocol Version 5 – Canada dated 10 February 2017) was also provided in Canada in order to include information related to gastrointestinal perforation reported for patients treated with alectinib, in order to be aligned with the approved Canadian product monograph.

Protocol deviations

Table 4: Major Protocol Deviations (Intent to Treat Population)

Protocol: BO28984
Study Population: Intent to Treat Population

Category Description	Crizotinib (N=151)	Alectinib (N=152)
Total number of patients with at least one major protocol deviation	33 (21.9%)	30 (19.7%)
Total number of major protocol deviations	52	51
INCLUSION CRITERIA		
FAILURE TO OBTAIN INFORMED CONSENT	1 (0.7%)	1 (0.7%)
BRAIN/LEPTOMENIGEAL DIS. NOT ASYMPT/TREATED/STABLE	1 (0.7%)	0
INADEQUATE HEMATOLOGIC FUNCTION AT BASELINE	0	1 (0.7%)
NOT A STAGE IIIB, NOT A STAGE IV	0	1 (0.7%)
MEDICATION		
CONTINUATION OF STUDY DRUG WHEN SHOULD BE DISC.	4 (2.6%)	4 (2.6%)
STUDY DRUG NOT ACC. TO ASSIGNED TREATMENT ARM	1 (0.7%)	1 (0.7%)
PROCEDURAL		
OMISSION OF DISEASE ASSESSMENT	10 (6.6%)	7 (4.6%)
FAILURE TO PERFORM TUMOR ASSESSMENT AS PER PROTOC.	7 (4.6%)	6 (3.9%)
NON REQUIRED TEST	4 (2.6%)	5 (3.3%)
DOSE NOT MODIFIED FOR TOXICITY ACC. TO PROTOCOL	4 (2.6%)	3 (2.0%)
OMISSION OF COMPLETE LABORATORY PANEL	1 (0.7%)	5 (3.3%)
WRONG ICF VERSION	2 (1.3%)	4 (2.6%)
SAES/AESIS/PREGNANCIES NOT REPORTED TIMELY	3 (2.0%)	2 (1.3%)
THE USE OF PROTOCOL-DEFINED PROHIBITED THERAPY	2 (1.3%)	1 (0.7%)
FAILURE TO OBTAIN SURVIVAL FOLLOW-UP	1 (0.7%)	1 (0.7%)

Data cutoff: 09 February 2017.

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Baseline data

Table 5: Demographic and Baseline Characteristics (Intent to Treat Population)

Protocol: BO28984
Study Population: Intent to Treat Population

	Crizotinib (N=151)	Alectinib (N=152)
Age (years)		
n	151	152
Mean (SD)	53.8 (13.5)	56.3 (12.0)
Median	54.0	58.0
Min - Max	18 - 91	25 - 88
Age group (years)		
n	151	152
< 65	118 (78.1%)	115 (75.7%)
>= 65	33 (21.9%)	37 (24.3%)
Sex		
n	151	152
Male	64 (42.4%)	68 (44.7%)
Female	87 (57.6%)	84 (55.3%)
Ethnicity		
n	151	152
Hispanic or Latino	8 (5.3%)	8 (5.3%)
Not Hispanic or Latino	136 (90.1%)	138 (90.8%)
Not Stated	7 (4.6%)	6 (3.9%)
Race		
n	151	152
American Indian or Alaska Native	0	4 (2.6%)
Asian	69 (45.7%)	69 (45.4%)
Black or African American	4 (2.6%)	0
Native Hawaiian or other Pacific Islander	1 (0.7%)	1 (0.7%)
White	75 (49.7%)	76 (50.0%)
Unknown	2 (1.3%)	2 (1.3%)
Weight (kg) at Baseline		
n	145	150
Mean (SD)	65.81 (13.20)	67.03 (15.81)
Median	64.60	65.35
Min - Max	42.0 - 108.0	40.4 - 131.5
Smoking Status at Screening		
n	151	152
Active Smoker	5 (3.3%)	12 (7.9%)
Non-Smoker	98 (64.9%)	92 (60.5%)
Past Smoker	48 (31.8%)	48 (31.6%)
ECOG Performance Status at Baseline		
n	151	152
0 or 1	141 (93.4%)	142 (93.4%)
2	10 (6.6%)	10 (6.6%)
Measurable/Non-Measurable CNS Lesions at Baseline (IRC)		
n	151	152
No	93 (61.6%)	88 (57.9%)
Yes	58 (38.4%)	64 (42.1%)

Data cutoff: 09 February 2017.

Table 6: Disease History of NSCLC (Intent to Treat Population)

Protocol: BO28984
Study Population: Intent to Treat Population

	Crizotinib (N=151)	Alectinib (N=152)
Time from Initial Diagnosis to Treatment Start (months)		
n	150	149
Mean (SD)	6.63 (17.26)	7.41 (16.86)
Median	1.91	1.68
Min - Max	0.5 - 155.7	0.4 - 105.0
Histologic Type		
n	151	152
Adenocarcinoma	142 (94.0%)	136 (89.5%)
Bronchioalveolar carcinoma	0	1 (0.7%)
Large cell carinoma	3 (2.0%)	0
Mixed with predominantly adenocarcinoma component	1 (0.7%)	0
Squamous cell carcinoma	2 (1.3%)	5 (3.3%)
Undifferentiated	0	4 (2.6%)
Other	3 (2.0%)	6 (3.9%)
Initial Stage of Disease		
n	151	152
I	2 (1.3%)	6 (3.9%)
IIA	7 (4.6%)	2 (1.3%)
IIB	1 (0.7%)	1 (0.7%)
IIIA	11 (7.3%)	12 (7.9%)
IIIB	11 (7.3%)	9 (5.9%)
IV	119 (78.8%)	122 (80.3%)
Stage of Disease at Baseline		
n	151	152
IIIB	6 (4.0%)	4 (2.6%)
IV	145 (96.0%)	148 (97.4%)
Local ALK Testing Method		
n	151	152
FISH	71 (47.0%)	50 (32.9%)
IHC	45 (29.8%)	50 (32.9%)
Polymerase Chain Reaction	4 (2.6%)	8 (5.3%)
Other	3 (2.0%)	4 (2.6%)
Not Done	28 (18.5%)	40 (26.3%)
Local ALK Test Result		
n	151	152
Positive	118 (78.1%)	109 (71.7%)
Negative	5 (3.3%)	3 (2.0%)
Not Done	28 (18.5%)	40 (26.3%)
Prior Chemotherapy for Localized Disease		
n	151	152
Yes	17 (11.3%)	13 (8.6%)
No	134 (88.7%)	139 (91.4%)
CNS Metastases by Investigator		
n	151	152
Yes	57 (37.7%)	60 (39.5%)
No	94 (62.3%)	92 (60.5%)
CNS Metastases Treatment		
n	22	27
Brain Surgery	1 (4.5%)	4 (14.8%)
Radiosurgery	4 (18.2%)	5 (18.5%)
Whole Brain Radiotherapy	15 (68.2%)	16 (59.3%)
Other	2 (9.1%)	2 (7.4%)
Prior Brain Radiation		
n	151	152
Yes	21 (13.9%)	26 (17.1%)
No	130 (86.1%)	126 (82.9%)

Data cutoff: 09 February 2017.

Numbers analysed

Protocol: BO28984
Study Population: Intent to Treat Population

	Crizotinib (N=151)	Alectinib (N=152)	Total (N=303)
Intent to Treat Population			
n (%)	151 (100.0%)	152 (100.0%)	303 (100.0%)
Safety Population			
n (%)	151 (100.0%)	152 (100.0%)	303 (100.0%)
Response Evaluable Population (Investigator)			
n (%)	151 (100.0%)	152 (100.0%)	303 (100.0%)
Response Evaluable Population (IRC)			
n (%)	145 (96.0%)	146 (96.1%)	291 (96.0%)
FISH Positive Population			
n (%)	97 (64.2%)	106 (69.7%)	203 (67.0%)
CNS Lesions at Baseline Based on RECIST:			
Patients with Measurable CNS Lesions	22 (14.6%)	21 (13.8%)	43 (14.2%)
Patients with Only Non-Measurable CNS Lesions	36 (23.8%)	43 (28.3%)	79 (26.1%)
Patients with No CNS Lesions	93 (61.6%)	88 (57.9%)	181 (59.7%)
PRO Evaluable Population			
n (%)	97 (64.2%)	100 (65.8%)	197 (65.0%)
ECG Evaluable Population			
n (%)	146 (96.7%)	144 (94.7%)	290 (95.7%)
PK Evaluable Population			
n (%)	0	144 (94.7%)	144 (47.5%)

Data cutoff: 09 February 2017.
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Outcomes and estimation

Primary endpoint

Progression-Free Survival (investigator-assessed)

Table 7: Time to Event Summary of Investigator-Assessed Progression Free Survival (Intent to Treat Population) - ALEX

	Crizotinib (N=151)		Alectinib (N=152)
Patients with event (%)	102 (67.5%)		62 (40.8%)
Earliest contributing event			
Death	12		8
Disease Progression	90		54
Patients without event (%)	49 (32.5%)		90 (59.2%)
Time to Event (months)			
Median	11.1		NE
95% CI	(9.1, 13.1)		(17.7, NE)
25% and 75%-ile	5.6, 22.2		7.6, NE
Range	0.0* to 25.8*		0.0* to 28.2*
Stratified Analysis			
p-value (log-rank)		<.0001	
Hazard Ratio		0.47	
95% CI		(0.34, 0.65)	
Unstratified Analysis			
p-value (log-rank)		<.0001	
Hazard Ratio		0.48	
95% CI		(0.35, 0.66)	
1 Year Duration			
Patients remaining at risk	65		97
Event Free Rate (%)	48.66		68.44
95% CI	(40.40, 56.92)		(60.97, 75.91)
Difference in Event Free Rate		-19.78	
95% CI		(-30.92, -8.65)	
p-value (Z-test)		0.0005	

* Censored, ^ Censored and event.
Summaries of PFS (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. Stratified hazard ratio and p-value are stratified for covariates Race (Asian vs Non-Asian) and CNS metastases at baseline by IRC.
Data cutoff: 09 February 2017.

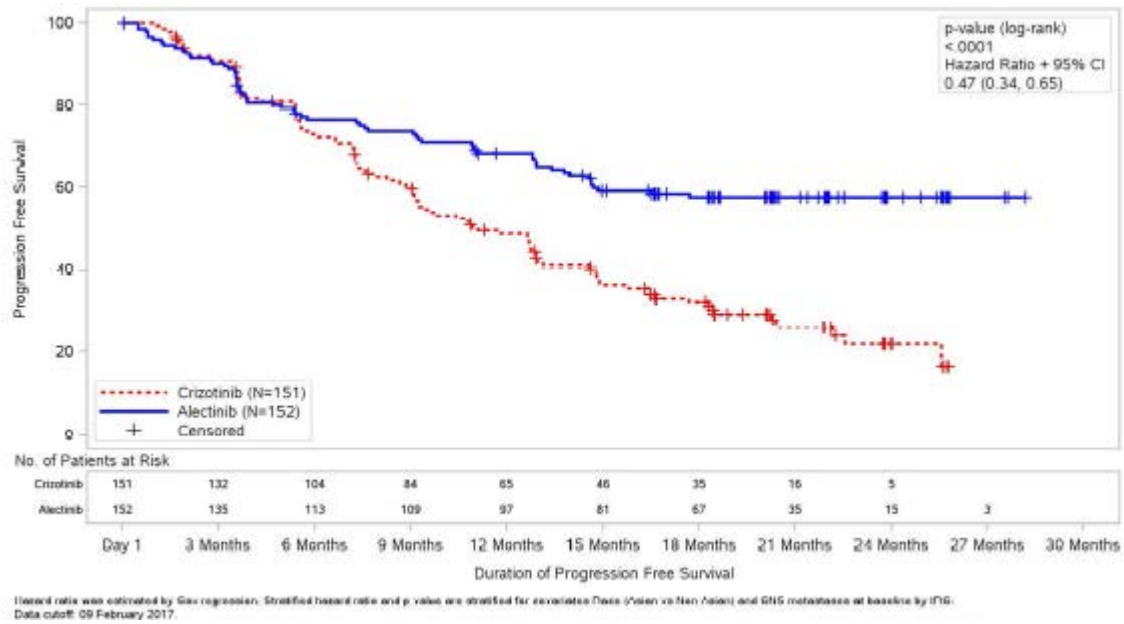


Figure 7: Kaplan-Meier Plot of Investigator-Assessed PFS (ITT Population)

Secondary endpoints

Progression-Free Survival (IRC-Assessed)

Table 8: Time to Event Summary of Progression Free Survival (IRC, RECIST) (Intent to Treat Population)

	Crizotinib (N=151)		Alectinib (N=152)
Patients with event (%)	92 (60.9%)		63 (41.4%)
Earliest contributing event			
Death	10		12
Disease Progression	82		51
Patients without event (%)	59 (39.1%)		89 (58.6%)
Time to Event (months)			
Median	10.4		25.7
95% CI	(7.7, 14.6)		(19.9, NE)
25% and 75%-ile	5.4, NE		7.1, NE
Range	0.0* to 25.8*		0.0* to 28.2*
Stratified Analysis			
p-value (log-rank)		<.0001	
Hazard Ratio		0.50	
95% CI		(0.36, 0.70)	
Unstratified Analysis			
p-value (log-rank)		<.0001	
Hazard Ratio		0.52	
95% CI		(0.38, 0.72)	
1 Year Duration			
Patients remaining at risk	57		95
Event Free Rate (%)	46.12		66.53
95% CI	(37.74, 54.50)		(58.95, 74.11)
Difference in Event Free Rate		-20.41	
95% CI		(-31.71, -9.11)	
p-value (Z-test)		0.0004	

* Censored, ^ Censored and event.
Summaries of PFS (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. Stratified hazard ratio and p-value are stratified for covariates Race (Asian vs Non-Asian) and CNS metastases at baseline by IRC.
Data cutoff: 09 February 2017.

Objective Response Rate

Table 9: Objective Response Rate (Investigator), (Intent to Treat Population, Response Evaluable Population)

	Crizotinib (N=151)		Alectinib (N=152)
Responders	114 (75.5%)		126 (82.9%)
95% CI for Response Rates	(67.84, 82.12)		(75.95, 88.51)
Diff. in Overall Response Rates (95% CI)		7.40 (-1.71, 16.50)	
Stratified Analysis			
p-value (Mantel-Haenszel Test)		0.0936	
Odds Ratio for Overall Response (95% CI)		1.62 (0.92, 2.84)	
Unstratified Analysis			
p-value (Mantel-Haenszel Test)		0.1132	
Odds Ratio for Overall Response (95% CI)		1.57 (0.90, 2.76)	
Complete Response (CR)	2 (1.3%)		6 (3.9%)
95% CI	(0.16, 4.70)		(1.46, 8.39)
Partial Response (PR)	112 (74.2%)		120 (78.9%)
95% CI	(66.43, 80.94)		(71.60, 85.13)
Stable Disease (SD)	24 (15.9%)		9 (5.9%)
95% CI	(10.46, 22.72)		(2.74, 10.94)
Progressive Disease (PD)	10 (6.6%)		8 (5.3%)
95% CI	(3.22, 11.84)		(2.30, 10.11)
Missing or Unevaluable	3 (2.0%)		9 (5.9%)

Response Evaluable Population is defined as patients with measurable disease at baseline according to the investigator. 95% CI for rates are calculated using Clopper-Pearson method. 95% CI for difference in rates and for odds ratio are constructed using the Wald method. P-values are calculated using the Mantel-Haenszel method. Patients were classified as "Stable Disease" if assessment was at least 7 weeks from baseline/study entry. Patients were classified as "unevaluable" if all post-baseline response assessments were reported as not evaluable, or SD assessment occurred within 7 weeks from baseline/study entry.
Patients were classified as "Missing" if no post-baseline response assessments were available.
Data cutoff: 09 February 2017.

Duration of Response

Table 10: Duration of Response (Investigator) (Intent to Treat Population, Response Evaluable Population)

	Crizotinib (N=151)		Alectinib (N=152)
Patients included in analysis (%)	114 (100.0%)		126 (100.0%)
Patients with event (%)	73 (64.0%)		40 (31.7%)
Earliest contributing event			
Death	7		1
Disease Progression	66		39
Patients without event (%)	41 (36.0%)		86 (68.3%)
Duration of Response (months)			
Median	11.1		NE
95% CI	(7.9, 13.0)		NE
25% and 75%-ile	5.6, 21.0		11.1, NE
Range	0.0* to 24.0*		1.2 to 26.5*
Stratified Analysis			
p-value (log-rank)		<.0001	
Hazard Ratio		0.36	
95% CI		(0.24, 0.53)	
Unstratified Analysis			
p-value (log-rank)		<.0001	
Hazard Ratio		0.36	
95% CI		(0.24, 0.53)	

* Censored, ^ Censored and event.
Summaries of Time-to-Event (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. Stratified hazard ratio and p-value are stratified for covariates Race (Asian vs Non-Asian) and CNS metastases at baseline by IRC.
Response Evaluable Population is defined as patients with measurable disease at baseline according to the investigator.
Data cutoff: 09 February 2017.

Overall survival

Table 11: Time to Event Summary of Overall Survival (Intent to Treat Population)

	Crizotinib (N=151)		Alectinib (N=152)
Patients with event (%)	40 (26.5%)		35 (23.0%)
Earliest contributing event			
Death	40		35
Patients without event (%)	111 (73.5%)		117 (77.0%)
Time to Event (months)			
Median	NE		NE
95% CI	NE		NE
25% and 75%-ile	17.1, NE		19.9, NE
Range	0.3* to 27.0*		0.5^ to 29.1*
Stratified Analysis			
p-value (log-rank)		0.2405	
Hazard Ratio		0.76	
95% CI		(0.48, 1.20)	
Unstratified Analysis			
p-value (log-rank)		0.3260	
Hazard Ratio		0.80	
95% CI		(0.51, 1.25)	
1 Year Duration			
Patients remaining at risk	103		119
Event Free Rate (%)	82.45		84.29
95% CI	(76.05, 88.85)		(78.39, 90.19)
Difference in Event Free Rate		-1.84	
95% CI		(-10.54, 6.87)	
p-value (Z-test)		0.6789	

* Censored, ^ Censored and event.
Summaries of Time-to-Event (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. Stratified hazard ratio and p-value are stratified for covariates Race (Asian vs Non-Asian) and CNS metastases at baseline by IRC.
Data cutoff: 09 February 2017.

CNS Efficacy

Time to CNS Progression by IRC RECIST

Table 12: Cause-Specific Hazard Ratios by IRC RECIST (ITT Population)

	Crizotinib N = 151	Alectinib N = 152
CNS progression without prior non-CNS progression		
Patients with events	68 (45%)	18 (12%)
Stratified analysis [a]		
Cause-specific HR [b]	0.16	
95% CI	(0.10, 0.28)	
p-value (log-rank)	<0.0001	
Non-CNS progression without prior CNS progression		
Patients with events	33 (22%)	36 (24%)
Stratified analysis [a]		
Cause-specific HR [b]	0.81	
95% CI	(0.49, 1.31)	
p-value (log-rank)	0.3832	
Death without prior CNS or non-CNS progression		
Patients with events	9 (6%)	11 (7%)
Stratified analysis [a]		
Cause-specific HR [b]	0.68	
95% CI	(0.26, 1.77)	
p-value (log-rank)	0.4307	

CI = confidence interval; CNS = central nervous system; HR = hazard ratio; IRC = Independent Review Committee; ITT = Intent-to-Treat; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors.

[a] Stratified by race (Asian vs. non-Asian) and CNS metastases at baseline by IRC.

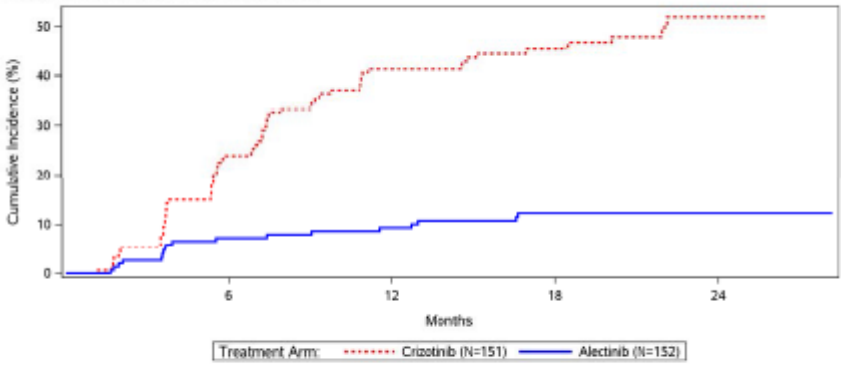
[b] Estimated by Cox regression.

Note: CNS and non-CNS progressions were evaluated independently, and therefore the total number of events does not match the number of PFS events.

Source: ALEX CSR, CTD Module 5.3.5.1: Table 15

g_ef_cif_CNSCIR_1_IRC_CREC_IT Cumulative Incidence Curves Based on RECIST (IRC) - CNS Progression without Prior Non-CNS Progression

Protocol: BO28984
Study Population: Intent to Treat Population



Competing risk analysis of CNS progression, non-CNS progression, and death as competing events.
Data cutoff: 09 February 2017.
Program: /opt/BIOSTAT/prod/cdpt7853/bo28984/g_ef_cif.sas
Output: /opt/BIOSTAT/prod/cdt7853/t28984a/reports/g_ef_cif_CNSCIR_1_IRC_CREC_IT.pdf
12APR2017 16:39

CNS = central nervous system; ITT = Intent-to-Treat.

Figure 8: Cumulative Incidence of CNS Progression by IRC RECIST (ITT Population)

CNS Objective Response Rate According to RECIST v1.1 Criteria

Table 13: Objective Response Rate (IRC, CNS RECIST) for Patients with Measurable CNS and Non-Measurable CNS Lesions at Baseline, (Intent to Treat Population)

	Crizotinib (N=58)		Alectinib (N=64)
Responders	15 (25.9%)		38 (59.4%)
95% CI for Response Rates	(15.26, 39.04)		(46.37, 71.49)
Diff. in Overall Response Rates (95% CI)		33.51 (17.03, 50.00)	
Stratified Analysis			
p-value (Mantel-Haenszel Test)		0.0002	
Odds Ratio for Overall Response (95% CI)		4.05 (1.89, 8.70)	
Unstratified Analysis			
p-value (Mantel-Haenszel Test)		0.0002	
Odds Ratio for Overall Response (95% CI)		4.19 (1.94, 9.06)	
Complete Response (CR)	5 (8.6%)		29 (45.3%)
95% CI	(2.86, 18.98)		(32.82, 58.25)
Partial Response (PR)	10 (17.2%)		9 (14.1%)
95% CI	(8.59, 29.43)		(6.64, 25.02)
Stable Disease (SD)	32 (55.2%)		16 (25.0%)
95% CI	(41.54, 68.26)		(15.02, 37.40)
Progressive Disease (PD)	6 (10.3%)		4 (6.3%)
95% CI	(3.89, 21.17)		(1.73, 15.24)
Missing or Unevaluable	5 (8.6%)		6 (9.4%)

95% CI for rates are calculated using Clopper-Pearson method. 95% CI for difference in rates and for odds ratio are constructed using the Wald method. P-values are calculated using the Mantel-Haenszel method.
Patients were classified as "Stable Disease" if assessment was at least 7 weeks from baseline/study entry. Patients were classified as "unevaluable" if all post-baseline response assessments were reported as not evaluable, or SD assessment occurred within 7 weeks from baseline/study entry.
Patients were classified as "Missing" if no post-baseline response assessments were available.
Data cutoff: 09 February 2017.

Table 14: Objective Response Rate (IRC, CNS RECIST) for Patients with Measurable CNS Lesions at Baseline, (Intent to Treat Population)

	Crizotinib (N=22)		Alectinib (N=21)
Responders	11 (50.0%)		17 (81.0%)
95% CI for Response Rates	(28.22, 71.78)		(58.09, 94.55)
Diff. in Overall Response Rates (95% CI)		30.95 (4.15, 57.76)	
Stratified Analysis			
p-value (Mantel-Haenszel Test)		0.0306	
Odds Ratio for Overall Response (95% CI)		4.34 (1.10, 17.17)	
Unstratified Analysis			
p-value (Mantel-Haenszel Test)		0.0354	
Odds Ratio for Overall Response (95% CI)		4.25 (1.08, 16.77)	
Complete Response (CR)	1 (4.5%)		8 (38.1%)
95% CI	(0.12, 22.84)		(18.11, 61.56)
Partial Response (PR)	10 (45.5%)		9 (42.9%)
95% CI	(24.39, 67.79)		(21.82, 65.98)
Stable Disease (SD)	7 (31.8%)		1 (4.8%)
95% CI	(13.86, 54.87)		(0.12, 23.82)
Progressive Disease (PD)	3 (13.6%)		2 (9.5%)
95% CI	(2.91, 34.91)		(1.17, 30.38)
Missing or Unevaluable	1 (4.5%)		1 (4.8%)

95% CI for rates are calculated using Clopper-Pearson method. 95% CI for difference in rates and for odds ratio are constructed using the Wald method. P-values are calculated using the Mantel-Haenszel method.
Patients were classified as "Stable Disease" if assessment was at least 7 weeks from baseline/study entry. Patients were classified as "unevaluable" if all post-baseline response assessments were reported as not evaluable, or SD assessment occurred within 7 weeks from baseline/study entry.
Patients were classified as "Missing" if no post-baseline response assessments were available.
Data cutoff: 09 February 2017.

CNS Duration of Response according to RECIST v1.1 Criteria

Table 15: CNS Duration of Response (IRC, CNS RECIST) for Patients with Measurable and Non-Measurable CNS Lesions at Baseline (Intent to Treat Population)

	Crizotinib (N=58)	Alectinib (N=64)
Patients included in analysis (%)	15 (100.0%)	38 (100.0%)
Patients with event (%)	13 (86.7%)	11 (28.9%)
Earliest contributing event		
Death	5	4
Disease Progression	8	7
Patients without event (%)	2 (13.3%)	27 (71.1%)
Duration of Response (months)		
Median	3.7	NE
95% CI	(3.2, 6.8)	(17.3, NE)
25% and 75%-ile	2.3, 17.3	13.4, NE
Range	1.9 to 18.1	1.5 to 22.2*
Stratified Analysis		
p-value (log-rank)	0.0002	
Hazard Ratio	0.23	
95% CI	(0.10, 0.53)	
Unstratified Analysis		
p-value (log-rank)	<.0001	
Hazard Ratio	0.22	
95% CI	(0.10, 0.50)	

* Censored, ^ Censored and event.
Summaries of Time-to-Event (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. Stratified hazard ratio and p-value are stratified for covariates Race (Asian vs Non-Asian) and CNS metastases at baseline by IRC.
Data cutoff: 09 February 2017.

Table 16: CNS Duration of Response (IRC, CNS RECIST) for Patients with Measurable CNS Lesions at Baseline (Intent to Treat Population)

	Crizotinib (N=22)	Alectinib (N=21)
Patients included in analysis (%)	11 (100.0%)	17 (100.0%)
Patients with event (%)	9 (81.8%)	6 (35.3%)
Earliest contributing event		
Death	2	1
Disease Progression	7	5
Patients without event (%)	2 (18.2%)	11 (64.7%)
Duration of Response (months)		
Median	5.5	17.3
95% CI	(2.1, 17.3)	(14.8, NE)
25% and 75%-ile	2.1, 17.3	14.8, NE
Range	1.9 to 18.1	1.5 to 20.3*
Stratified Analysis		
p-value (log-rank)	0.1084	
Hazard Ratio	0.42	
95% CI	(0.15, 1.24)	
Unstratified Analysis		
p-value (log-rank)	0.0921	
Hazard Ratio	0.41	
95% CI	(0.14, 1.19)	

* Censored, ^ Censored and event.
Summaries of Time-to-Event (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. Stratified hazard ratio and p-value are stratified for covariates Race (Asian vs Non-Asian) and CNS metastases at baseline by IRC.
Data cutoff: 09 February 2017.

Patient reported outcomes (PRO)

Baseline compliance for both treatment arms was moderate in the ITT population with about 65 % (similar in both arms) completing their baseline assessment. According to the MAH the reason was due to suboptimal initial site training to introduce the electronic device used for reporting, to the patients.

Among patients who had PRO baseline data, moderate-to-high compliance rates (≥ 60%) throughout the study except for Weeks 112 and 116 were observed in the alectinib arm whereas compliance rates in the crizotinib arm dropped to ≤60% from Week 68 onwards except for Weeks 120 through128, when one patient remained on treatment. On average, patients in the alectinib arm reported clinically meaningful improvement in HRQoL earlier (Week 8 vs. Week 12), and for a longer duration of time (until Week 88 vs. Week 68), than patients in the crizotinib arm. Patient-reported outcome data suggest greater tolerability with alectinib for commonly reported treatment-related symptoms including diarrhoea, constipation, peripheral neuropathy, nausea/vomiting, appetite loss, and dysphagia as compared with crizotinib.

Both treatment arms demonstrated clinically meaningful improvement (≥ 10-point decrease) in multiple lung cancer symptoms, including patient-reported cough, chest pain, pain in other parts, fatigue, and dyspnoea (single-item scale). It is however recognised that patients in the alectinib arm reported symptomatic improvement for a longer duration of time than patients in the crizotinib arm.

For the subgroup of patients with CNS metastases at baseline, a lower proportion (≥ 10% difference) of patients in the alectinib arm reported clinically meaningful worsening in HRQoL compared with crizotinib, starting at Week 12 (4% alectinib vs. 16% crizotinib) and persisting for most assessments through Week 84 (0% alectinib vs. 17% crizotinib). Although limited differences between treatment arms were seen in cognitive functioning in the PRO-evaluable population, a benefit with alectinib was shown within the pre-specified subgroup of patients with CNS metastases at baseline. Fewer patients receiving alectinib reported clinically meaningful worsening in cognitive functioning compared with crizotinib, starting at Week 4 (8% vs. 27%) and continuing through Week 84 (10% vs. 33%).

Ancillary analyses

Sensitivity Analyses

The results of the pre-specified sensitivity analysis which applied alternative censoring rules, were consistent with the primary efficacy analysis, demonstrating superiority of alectinib over crizotinib in reducing the risk of disease progression or death (investigator-assessed PFS) by 60% (HR 0.40; 95% CI: 0.28-0.58; $p < 0.0001$).

	Crizotinib (N=151)		Alectinib (N=152)
Patients with event (%)	86 (57.0%)		45 (29.6%)
Earliest contributing event			
Death	4		2
Disease Progression	82		43
Patients without event (%)	65 (43.0%)		107 (70.4%)
Time to Event (months)			
Median	12.7		NE
95% CI	(9.6, 15.7)		NE
25% and 75%-ile	5.9, 25.6		12.8, NE
Range	0.0* to 25.8*		0.0* to 28.2*
Stratified Analysis			
p-value (log-rank)		<.0001	
Hazard Ratio		0.40	
95% CI		(0.28, 0.58)	
Unstratified Analysis			
p-value (log-rank)		<.0001	
Hazard Ratio		0.41	
95% CI		(0.28, 0.58)	
1 Year Duration			
Patients remaining at risk	62		95
Event Free Rate (%)	53.12		75.21
95% CI	(44.57, 61.67)		(67.96, 82.45)
Difference in Event Free Rate		-22.09	
95% CI		(-33.29, -10.88)	
p-value (Z-test)		0.0001	

* Censored, ^ Censored and event.
Summaries of Time-to-Event (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. Stratified hazard ratio and p-value are stratified for covariates Race (Asian vs Non-Asian) and CNS metastases at baseline by IRC.
Patients are censored at the last overall response assessment before PD or Death if either patient received non-protocol anti-cancer therapy before PD or Death or patient was discontinued from treatment before PD or Death (not because of PD or Death) or patient had two or more consecutive missing overall response assessments before PD or Death.
Data cutoff: 09 February 2017.

Figure 9: **Time to Event Summary of Investigator-Assessed Progression Free Survival –Sensitivity Analysis (Intent to Treat Population)**

Results of the following additional sensitivity analyses of the primary endpoint using different censoring rules were also consistent with those of the primary analysis:

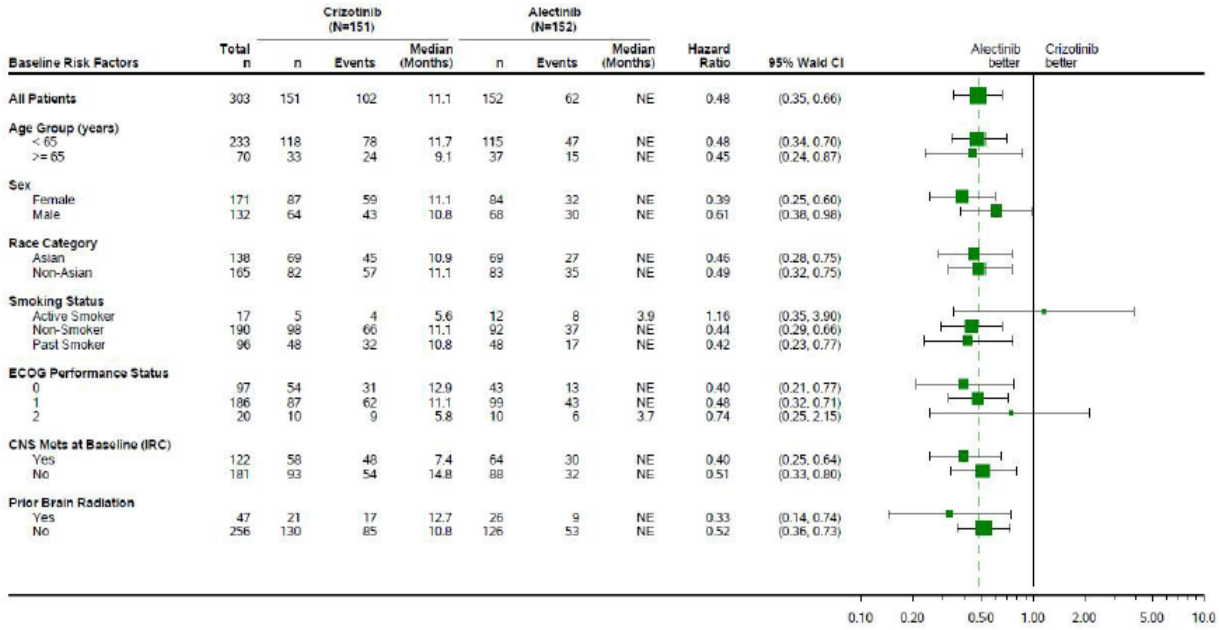
- Sensitivity analysis based on the stratification factors entered at randomization in the IxRS: HR 0.48; 95% CI: 0.35-0.66; p < 0.0001

- Sensitivity analysis to assess the effect of missing tumour assessments:

HR 0.47; 95% CI: 0.34-0.65; p < 0.0001

- Sensitivity analysis to assess the effect of patients lost to follow-up:

HR 0.48; 95% CI: 0.35-0.66; p < 0.0001.



Medians of PFS are Kaplan-Meier estimates. Hazard ratios were estimated by Cox regression.
Data cutoff: 09 February 2017.

Figure 10: **Forest Plot of Hazard Ratio for PFS (Investigator) by Subgroup, Unstratified Analysis (Intent to Treat Population)**

Summary of main study

The following table summarises 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 17: Summary of Efficacy for trial ALEX

Title: A randomized, multicentre, Phase III, open-label study of alectinib versus crizotinib in treatment-naïve ALK-positive advanced NSCLC			
Study identifier	BO28984		
Design	Open-label, randomised, comparative study		
	Duration of main phase:		
Hypothesis	Superiority		
Treatments groups	Alectinib		600 mg BID alectinib, orally continuously (cycles of 28 days) until disease progression, death, or withdrawal, number randomized: 152 patients
	Crizotinib		250 mg crizotinib BID, orally continuously (Cycles of 28 days) until disease progression, death, or withdrawal, number randomized: 151 patients
Endpoints and definitions	Primary endpoint	PFS by INV	Progression-free survival
	Key secondary endpoint	PFS by IRC	Progression-free survival

	Secondary endpoints other	Time to CNS progression (IRC) ORR (INV) OS DoR (INV) CNS ORR CNS DoR	 Overall response rates Overall survival Duration of response CNS Overall response rates by IRC CNS Duration of response by IRC
Database lock	31 March 2017		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Crizotinib	Alectinib	Hazard ratio
	Number of subjects	n=151	n=152	NA
	PFS (INV) (Months)	11.1	NE	0.47
	95% CI	[9.1-13.1]	[17.7-NE]	[0.34-0.65]
	PFS (IRC) (Months) 95% CI	10.4 [7.7-14.6]	25.7 [19.9-NE]	0.50 [0.36-0.70]
	OS (Months)	NR	NR	NA
	ORR (%)	76 %	83 %	NA
	95% CI	[67.8-82.1]	[76.0-88.5]	NA
	DOR (Months) 95% CI	11.1 [7.9-13.0]	NE NE	

Clinical studies in special populations

See Figure 10.

Supportive studies

Study JO28928 (J-ALEX)

An open-label, randomized Phase III study comparing alectinib head to head to crizotinib in patients who were ALK-inhibitor naïve but may have had received up to one prior chemotherapy regimen for ALK–positive NSCLC.

J-ALEX was conducted in an all Japanese population.

Treatments

Experimental arm (N=103): alectinib 300 mg BID

Control arm (N=104): crizotinib 250 mg BID (EU approved dose, Xalkori SmPC).

Randomisation

J-ALEX: A total of 207 patients were randomised in a 1:1 design to either crizotinib or alectinib by stratified permuted-block method using the following 3 factors, as stratification factors:

1) ECOG PS (0 or 1 vs. 2)
2) Treatment line (1st line vs. 2nd line)
3) Disease stage (IIIB/IV vs. post-operative recurrence).

Baseline and disease characteristics

The study population essentially reflects the ALK-positive NSCLC population i.e. diagnosed at a younger age than observed in the general NSCLC population, predominantly women and non-smokers with adenocarcinoma as expected, the dominating histology.

Endpoints

Primary endpoint: PFS by Independent review

Secondary endpoints: PFS by investigator, ORR (IRF), DoR (IRF), TTR (IRF), OS, Time to CNS progression in patients with CNS metastases at baseline, Time to onset of CNS metastases in patients without CNS metastases at baseline, Health-related QoL

Results

The initial submitted data was based on the results of the 2nd interim analysis with the cut-off date of December 3, 2015 when about 50% (83 events) of the required PFS events were reported whereby the iDMC recommended early study termination based on the efficacy. The median duration of follow-up at the time of this analysis was 12 months (range: 1 to 23 months) for the alectinib arm and 12 months (range: 0 to 20 months) for the crizotinib arm.

The study met its primary endpoint of superiority of alectinib over crizotinib in the first-line setting of ALK-inhibitors, with an improvement and at least a doubling of the PFS from median 10.2 months to NE (95%CI: 20.3-NE) resulting in HR 0.34. IRF-assessed ORR was 68.9% vs 76.7%, which is in line with other ALK-inhibitors and lower than in the phase I/II study. Time to response was similar in both arms but DOR was markedly longer with alectinib (11.1 months vs NE, HR 0.32).

The Applicant has as requested, provided an updated analysis with the cut-off date of 30 September 2016 meaning an additional 10 months of follow-up.

Table 18: IRF-assessed PFS per RECIST v1.1 (ITT population)

	Primary Analysis		Updated Analysis	
	Crizotinib n = 104	Alectinib n = 103	Crizotinib n = 104	Alectinib n = 103
IRF-assessed PFS				
Patients with events (%)	58 (56)	25 (24)	74 (71)	42 (41)
Median (months) (95% CI)	10.2 (8.2, 12.0)	NE (20.3, NE)	10.2 (8.3, 12.0)	25.9 (20.3, NE)
Stratified HR (99.6826% CI)	0.34 (0.17, 0.71)		0.38 (0.26, 0.55) [a]	
p-value	< 0.0001		< 0.0001 [b]	
12-month PFS				
Event-free rate (%) (95% CI)	40 (29.1, 50.8)	72 (61.9, 82.6)	43 (33.1, 52.4)	75 (66.4, 83.2)

Table 19: Investigator-assessed PFS per RECIST v1.1 (ITT population)

	Primary Analysis		Updated Analysis	
	Crizotinib n = 104	Alectinib n = 103	Crizotinib n = 104	Alectinib n = 103
Patients with events (%)	58 (56)	25 (24)	73 (70)	40 (39)
Median (months) (95% CI)	10.2 (6.5, 12.1)	NE (NE)	11.8 (8.1, 13.7)	28.6 (25.2, NE)
Stratified HR (95% CI)	0.34 (0.21, 0.54)		0.35 (0.23, 0.52)	

Table 20: IRF-assessed DOR per RECIST v1.1 (ITT population)

	Primary Analysis		Updated Analysis	
	Crizotinib (n = 71)	Alectinib (n = 79)	Crizotinib (n = 71)	Alectinib (n = 79)
Patients with events (%)	35 (49)	14 (18)	46 (65)	28 (35)
Median (95% CI)	11.1 (7.5, 13.1)	NE (NE)	11.1 (8.4, 15.9)	NE (21.4, NE)
Stratified HR (95% CI)	0.32 (0.17, 0.60)		0.39 (0.24, 0.63)	

Table 21: Time to IRF-assessed progression of brain metastases excluding death: ITT population

	Primary Analysis		Updated Analysis	
	Crizotinib (n = 29)	Alectinib (n = 14)	Crizotinib (n = 29)	Alectinib (n = 14)
Patients with event (%)	10 (35)	1 (7)	12 (41)	4 (29)
Median (95% CI)	NE (8.3, NE)	NE (NE)	16.7 (8.3, NE)	NE (25.9, NE)
Stratified HR (95% CI)	0.16 (0.02, 1.28)		0.51 (0.16, 1.64)	

AF-001JP

This Phase I/II Japanese study supports the results from the J-ALEX study. Primary endpoint was ORR by IRF (~94 %). Secondary endpoints PFS by IRF and OS are still relatively immature at the data cut-off date (39 % and 28 % event rate respectively) (data not shown).

2.4.3. Discussion on clinical efficacy

Alectinib received a conditional market authorisation in February 2017 based on data from two Phase I/II studies (studies NP28673 and NP28761) evaluating alectinib in ALK-positive NSCLC patients who had progressed on crizotinib (EMEA/H/C/4164). The specific obligation linked to the CMA is the submission of the ALEX CSR.

This variation concerns the extension of indication to first-line treatment of patients with ALK-positive advanced NSCLC. Initially only data from the ongoing Japanese Phase III J-ALEX study and from the Phase I/II AF-001JP study were submitted. However, in response to the request for supplementary information, the MAH provided data from the primary analysis from the ALEX study and as a consequence, requested a conversion of conditional to full marketing authorization within the context of this procedure.

Design and conduct of clinical studies

The ALEX study is considered the main study in this assessment as the dosing of alectinib is the EU approved dose i.e 600 mg BID. The CSR covers the study period of 19 August 2014 until data cut-off for the primary analysis on 9 February 2017. Data base lock occurred on the 31 March 2017.

A total of 303 patients were enrolled in the ALEX study and randomised in a 1:1 design to either alectinib 600 mg BID (N=152) or crizotinib (N=151). Both doses are according to their respective label (Alecenca SmPC and Xalkori SmPC respectively).

The inclusion and exclusion criteria are non-controversial thus raising no concern.

The dose of 600 mg BID was reviewed in the initial application for licensure and at that point considered reasonably well justified.

The ALEX study provides further support of the higher dose as PK/PD data shows that higher exposure seemingly is related to improved outcome. Thus the selected dose is considered justified.

In terms of baseline and disease characteristics, the study population essentially reflects the ALK-positive NSCLC population i.e. diagnosed at a younger age than observed in the general NSCLC population, predominantly women and non-smokers with adenocarcinoma the dominating histology. The vast majority had Stage IV disease at baseline (97%) and > 90 % had ECOG PS 0 or 1. Baseline and disease characteristics are largely well balanced.

Efficacy data and additional analyses

The study met its primary endpoint with a risk reduction for disease progression or death with 53% compared with crizotinib (HR=0.47, 95%CI:0.34, 0.65, p value < 0.0001) and the estimated median PFS was 11 months in the crizotinib arm whilst not yet reached in the alectinib arm. The K-M curves separates at about 6 months of treatment and remain clearly separated. This is well in line with previous observations in the J-ALEX study. PFS by IRC (key secondary endpoint) is consistent with the findings from the primary endpoint (HR 0.50 [95% CI: 0.36-0.70; stratified log-rank p < 0.0001]). The median PFS was 10 months in the crizotinib arm and approximately 26 months in the alectinib arm.

The sensitivity analyses support the result in the primary analysis and the treatment effect was consistent across the majority of pre-specified subgroups albeit the limited number of patients in some of them must be taken into consideration.

The secondary endpoint Time to CNS progression by IRC clearly demonstrates the superiority of alectinib over crizotinib in this patient population. The HR is 0.16 (0.10, 0.28), p value < 0.0001. The OS data are not yet mature, but there is a numerical difference in patients with events in favour of alectinib.

In terms of ORR, the proportion of responders (by INV) was 83% in the alectinib arm and 76% in the crizotinib arm. The difference in ORR of 7.4% (95% CI b [-1.71%, 16.50%]) for this key secondary endpoint was not statistically significant (p < 0.0936).

At the time of data cut-off, the median DOR was 11 months in the crizotinib arm and had not yet been reached in the alectinib arm.

In regard to overall survival, 27% of patients in the crizotinib arm and 23% of patients in the alectinib arm had died at the time of data cutoff, and median OS was not estimable in either arm. As the previous key secondary endpoint of investigator assessed ORR in the pre specified hierarchy was not statistically significant, OS was not formally tested for statistical significance (HR 0.76 [95% CI: 0.48, 1.20]). An OS follow up analysis is planned when approximately 50% of patients (i.e. 143 patients) have died.

The cumulative incidence of CNS progression was consistently lower across time in the alectinib arm compared with the crizotinib arm. This is indeed of clinical relevance. In terms of CNS response rate, in patients with measurable and non-measurable CNS lesions at baseline, more patients in the alectinib arm achieved a CNS response (59%) compared with crizotinib (26%). There were also more patients in the alectinib arm (45%) that achieved a CNS complete response compared with crizotinib (9%). Likewise, in patients with measurable CNS lesions at baseline, more patients in the alectinib arm achieved a CNS response (81%) compared with crizotinib (50%) with 38 % of the patients achieving CR in the alectinib arm as compared to the crizotinib arm (~5%).

A benefit favouring alectinib to crizotinib was also observed in regard to CNS response duration with a median of 17 months for alectinib treated patients compared with~ 6 months for patients in the crizotinib arm among CNS responders with measurable CNS lesions at baseline. In patients with measurable and non-measurable CNS lesions at baseline, the median CNS DOR had not yet been reached in the alectinib arm at the time of the data cut-off whilst the median CNS DOR in the crizotinib arm was about 4 months. These results are indeed clinical relevant however, the limited number of patients included in the analyses is recognised.

In terms of HQoL/PRO results, baseline compliance for both treatment arms was moderate (~65 % completing their baseline assessment). PRO results are suggestive of increased tolerability for alectinib compared to crizotinib including commonly reported treatment-related symptoms (e.g. GI-related) although the open-label design should be taken into consideration.

During the review, the MAH was requested to discuss if there are any predictive factors that could help to identify resistance to alectinib. As of today no factors that would predict resistance to alectinib or any other ALK inhibitor in the first-line setting have been identified. However there is preliminary evidence that knowledge of the ALK variant may provide valuable information if patients may develop ALK dependent resistance. Resistance to ALK TKI treatment, either acquired secondary ALK mutations or activation of ALK independent pathways (Isozaki et al 2016; Dong et al 2016) like EGFR pathway activation, is considered to be the result of the selective pressure on the tumour caused by ALK TKI treatment.

Eligible patients in the ALEX study were to have histological or cytological confirmed diagnosis of advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) ALK-positive NSCLC. Although the study enrolled mainly patients with Stage IV disease (80 %), there is no reason to question similar anti-tumour activity in patients with Stage III disease reason why it was considered appropriate to follow the same wording of indication as previously adopted for the second line setting and for other ALK inhibitors.

Supportive studies

The results from the ALEX study are supported by data from the Japanese J-ALEX study and the Phase I/II AF-001JP study. These two studies were already included and reviewed in the initial application for licensure (EMEA/H/C/4164). J-ALEX is an open-label, randomized (1:1), Phase III study comparing the efficacy and safety of crizotinib 250 mg BID (EU approved dose) versus alectinib 300 mg BID (Japanese approved dose) in patients who were ALK inhibitor – naïve. Patients could have received up to one prior chemotherapy regimen. A total of 207 patients were included (103 in the alectinib arm and 104 in the crizotinib arm).

The study met its primary endpoint of superiority of alectinib over crizotinib in the first-line setting of ALK-inhibitors, with an improvement and at least a doubling of the PFS from median 10.2 months to NE (95%CI: 20.3-NE) resulting in HR 0.34. IRF-assessed ORR was 68.9% vs 76.7%, which is in line with other ALK-inhibitors and lower than in the phase I/II study. Time to response was similar in both arms but DOR was markedly longer with alectinib (11.1 months vs NE, HR 0.32). The Applicant has provided an updated analysis with the cut-off date of 30 September 2016 meaning an additional 10 months of follow-up. The updated PFS data continue to be in favour of alectinib and in line with the primary analysis. While PFS data in the crizotinib can be considered mature, the number of patients with events in the alectinib arm (41%) is still considered immature. The OS data are also considered immature, but with a trend in favour of alectinib.

Although promising results on CNS efficacy the data were immature. An update has been provided and the updated efficacy data continues to support the primary analysis. Patient with brain metastases that are treated with alectinib continue to be at lower risk of progression of CNS metastases. In patients with no CNS metastases at baseline, alectinib continues to show a clear benefit. Having in mind that these lung cancer patients often relapse due to CNS metastases, alectinib seems to provide an advantage in terms of PFS.

In the Phase I/II AF-001JP study primary endpoint was ORR by IRF (~94 %). Secondary endpoints PFS by IRF and OS are still relatively immature at the data cut-off date (39 % and 28 % event rate respectively).

Considering the results from the ALEX study, the efficacy of alectinib in first-line is considered demonstrated.

2.4.4. Conclusions on the clinical efficacy

In the previous submitted data from the Japanese, crizotinib comparative J-ALEX study a convincing benefit of alectinib over that of crizotinib was demonstrated. With the data now available from the primary analysis of the global ALEX study which uses the EU-approved alectinib dose of 600 mg BID, the superiority of alectinib over crizotinib in treatment-naïve patients with advanced ALK-positive NSCLC has been further substantiated. The treatment effect of alectinib on CNS metastases is compelling and of high clinical relevance.

The MAH is recommended to submit the final OS analysis for the ALEX study.

2.5. Clinical safety

Introduction

Safety data are available from a total of 303 patients in the ALEX study (N=152 alectinib; N=151 crizotinib). All patients in the ITT population received at least one dose of assigned study drug and were included in the safety population.

Supportive safety data were also provided from the Phase III J-ALEX study (103 patients in alectinib arm and 104 patients in crizotinib arm).

Patient exposure

The median duration of treatment was 18 months (range: 0-29 months) in the alectinib arm as compared with 11 month (range: 0-27 months) in the crizotinib arm. The proportion of patients that completed > 12 months of treatment was 66 % and 45 % for alectinib and crizotinib respectively and 49 % and 27 % completed > 18 months respectively. The mean dose intensity was comparable between treatment arms (92% for crizotinib and 96% for alectinib).

Table 22: **Study Treatment Exposure (Safety Population)**

	Crizotinib (N=151)	Alectinib (N=152)
Treatment duration (months)		
n	151	152
Mean (SD)	11.8 (7.7)	15.0 (8.7)
Median	10.7	17.9
Min - Max	0 - 27	0 - 29
Treatment duration (months)		
n	151	152
0 - <=6	48 (31.8%)	38 (25.0%)
>6 - <=12	35 (23.2%)	14 (9.2%)
>12 - <=18	27 (17.9%)	26 (17.1%)
>18 - <=24	30 (19.9%)	52 (34.2%)
>24 - <=30	11 (7.3%)	22 (14.5%)
Dose intensity (%)		
n	151	152
Mean (SD)	92.4 (14.1)	95.6 (10.3)
Median	100.0	100.0
Min - Max	42 - 107	45 - 100
Number of doses		
n	151	152
Mean (SD)	694.0 (465.1)	904.1 (525.4)
Median	617.0	1085.5
Min - Max	4 - 1646	26 - 1734
Total cumulative dose (mg)		
n	151	152
Mean (SD)	168301.0 (111989.8)	521320.1 (305243.2)
Median	148000.0	595800.0
Min - Max	1000 - 411500	15600 - 1036800
Missed doses		
n	151	152
No missed doses	87 (57.6%)	103 (67.8%)
At least one missed dose	64 (42.4%)	49 (32.2%)

Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day. Dose intensity is the amount of study drug actually received divided by the expected amount.
Data cutoff: 09 February 2017.

Adverse events

Table 23: Overview of safety (safety population):

	Crizotinib N = 151	Alectinib N = 152
Total number of patients with ≥ 1 AE	146 (97%)	147 (97%)
Total number of events, n	1365	1196
Total number of patients with ≥ 1		
AE with fatal outcome (Grade 5)	7 (5%)	5 (3%)
Grade ≥3 AE	76 (50%)	63 (41%)
Serious AE	44 (29%)	43 (28%)
Related AE	134 (89%)	117 (77%)
AE leading to treatment discontinuation	19 (13%)	17 (11%)
AE leading to drug interruption	38 (25%)	29 (19%)
AE leading to dose reduction	31 (21%)	24 (16%)

AE = adverse event.

The most common SOCs (≥ 30% of patients in either arm) in which AEs were reported were (crizotinib vs. alectinib):

- GI disorders (80% vs. 55%)
- General disorders and administration site conditions (57% vs. 51%)
- Investigations (46% each)
- Nervous system disorders (45% vs. 26%)
- Eye disorders (33% vs. 8%)
- Infections and infestations (30% vs. 40%)
- Respiratory, thoracic and mediastinal disorders (30% vs. 32%)
- Musculoskeletal and connective tissue disorders (28% vs. 36%)

Table 24: Adverse Events with an Incidence Rate of at Least 10% in Either Treatment Arm (Safety Population)

MedDRA System Organ Class MedDRA Preferred Term	Crizotinib (N=151)	Alectinib (N=152)
Total number of patients with at least one adverse event	132 (87.4%)	119 (78.3%)
Overall total number of events	601	405
GASTROINTESTINAL DISORDERS		
Total number of patients with at least one adverse event	112 (74.2%)	67 (44.1%)
Total number of events	314	126
CONSTIPATION	49 (32.5%)	52 (34.2%)
NAUSEA	72 (47.7%)	21 (13.8%)
DIARRHOEA	68 (45.0%)	18 (11.8%)
VOMITING	58 (38.4%)	11 (7.2%)
GENERAL DISORDERS AND AIMINISTRATION SITE CONDITIONS		
Total number of patients with at least one adverse event	57 (37.7%)	47 (30.9%)
Total number of events	75	64
OEDEMA PERIPHERAL	42 (27.8%)	26 (17.1%)
FATIGUE	25 (16.6%)	29 (19.1%)
INVESTIGATIONS		
Total number of patients with at least one adverse event	47 (31.1%)	40 (26.3%)
Total number of events	102	88
ALANINE AMINOTRANSFERASE INCREASED	45 (29.8%)	23 (15.1%)
ASPARTATE AMINOTRANSFERASE INCREASED	37 (24.5%)	21 (13.8%)
BLOOD BILIRUBIN INCREASED	2 (1.3%)	23 (15.1%)
NERVOUS SYSTEM DISORDERS		
Total number of patients with at least one adverse event	47 (31.1%)	16 (10.5%)
Total number of events	55	21
DIZZINESS	21 (13.9%)	12 (7.9%)
DYSGEUSIA	29 (19.2%)	4 (2.6%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Total number of patients with at least one adverse event	14 (9.3%)	36 (23.7%)
Total number of events	14	48
ARTHRALGIA	11 (7.3%)	17 (11.2%)
MYALGIA	3 (2.0%)	24 (15.8%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Total number of patients with at least one adverse event	7 (4.6%)	30 (19.7%)
Total number of events	7	37
ANAEMIA	7 (4.6%)	30 (19.7%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Total number of patients with at least one adverse event	14 (9.3%)	17 (11.2%)
Total number of events	15	19
RASH	14 (9.3%)	17 (11.2%)
EYE DISORDERS		
Total number of patients with at least one adverse event	18 (11.9%)	2 (1.3%)
Total number of events	19	2
VISUAL IMPAIRMENT	18 (11.9%)	2 (1.3%)

Investigator text for AEs encoded using MedDRA version 19.1. 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. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. Data cutoff: 09 February 2017.

Table 25: Grade 3 or Higher Adverse Events with a Difference in Incidence of at Least 2% between Treatment Arms (Safety Population)

MedDRA Preferred Term, n (%)	Crizotinib N = 151	Alectinib N = 152
Alanine aminotransferase increased	22 (15%)	7 (5%)
Aspartate aminotransferase increased	16 (11%)	8 (5%)
Neutropenia	6 (4%)	0
Pulmonary embolism	5 (3%)	2 (1%)
ECG QT prolonged	5 (3%)	0
Nausea	5 (3%)	1 (1%)
Vomiting	5 (3%)	0
Diarrhoea	3 (2%)	0
Pneumonitis	3 (2%)	0
Anaemia	1 (1%)	7 (5%)
Urinary tract infection	1 (1%)	4 (3%)
Acute kidney injury	0	4 (3%)
Blood bilirubin increased	0	3 (2%)
Lung infection	0	3 (2%)

AE = adverse event.

Note: Investigator text for AEs was encoded using MedDRA version 19.1. Percentages were based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual were counted only once.

Grade 3 elevation of CPK was reported for 2.6% of patients receiving alectinib and 1.3% of patients receiving crizotinib; and median time to Grade 3 CPK elevation was 27.5 days and 369 days, respectively, in the pivotal phase III clinical trial BO28984 (ALEX).

Adverse drug reactions

Adverse drug reactions were identified based on the collective assessment of AE data from clinical trials, non-clinical data, the causal relationship for AEs, and the drug's mechanism of action.

Pooled data from across the Phase II studies (NP28761, NP28673) and Phase III Study BO28984 (ALEX) have been included. The alectinib exposed patient population in the pooled Phase II studies and ALEX includes all patients who received at least one dose of alectinib, as follows:

- NP28761 and NP28673: N = 253 patients treated with alectinib 600 mg twice daily (BID) (data cutoff dates of 22 January 2016 for Study NP28761 and 01 February 2016 for Study NP28673)
- ALEX: N = 152 patients treated with alectinib 600 mg BID (data cut-off date of 09 February 2017).

Thus, the denominator for the calculation of incidences of ADRs accounts for 405 patients treated with alectinib 600 mg BID.

Increased weight, acute kidney injury, dysgeusia and stomatitis were the newly identified ADRs.

Table 26: ADRs reported in Alecensa clinical trials (N=405) and during post-marketing

System organ class ADRs (MedDRA)	**Alecensa N=405**		
	All grades (%)	**Frequency category (all grades)**	**Grades 3-4 (%)**
Blood and lymphatic system disorders			
Anaemia[1)]	17	Very common	3.0
Nervous system disorders			
Dysgeusia [2)]	5.2	Common	0.2
Eye disorders			
Vision disorders[3)]	8.6	Common	0
Cardiac disorders			
Bradycardia[4)]	8.9	Common	0
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease / pneumonitis	0.7	Uncommon	0.2
Gastrointestinal disorders			
Constipation	35	Very common	0
Nausea	19	Very common	0.5
Diarrhoea	16	Very common	0.7
Vomiting	11	Very common	0.2
Stomatitis [5)]	3.0	Common	0
Hepatobiliary disorders			
Increased bilirubin[6)]	18	Very common	3.2
Increased AST	15	Very common	3.7
Increased ALT	14	Very common	3.7
Increased alkaline phosphatase**	6.2	Common	0.2
Drug-induced liver injury[7)]	0.7	Uncommon	0.7
Skin and subcutaneous tissue disorders			
Rash[8)]	18	Very common	0.5
Photosensitivity	9.1	Common	0.2
Musculoskeletal and connective tissues disorders			
Myalgia[9)]	28	Very common	0.7
Increased blood creatine phosphokinase	10	Very common	3.2
Renal and urinary disorders			
Blood creatinine increased	7.2	Common	0.7*
Acute kidney injury	1.0	Common	1.0*
General disorders and administration site conditions			
Oedema[10)]	30	Very common	0.7
Investigations			
Weight increased	12	Very common	0.7

* Includes one Grade 5 event

** Increased alkaline phosphatase was reported in the post-marketing period and in pivotal phase II and phase III clinical trials.

[1)] includes cases of anaemia and haemoglobin decreased

[2)] includes cases of dysgeusia and hypogeusia

[3)] includes cases of blurred vision, visual impairment, vitreous floaters, reduced visual acuity, asthenopia, and diplopia

[4)] includes cases of bradycardia and sinus bradycardia

[5)] includes cases of stomatitis and mouth ulceration

[6)] includes cases of blood bilirubin increased, hyperbilirubinaemia and bilirubin conjugated increased

[7)] 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

[8)] includes cases of rash, rash maculopapular, dermatitis acneiform, erythema, rash generalised, rash papular, rash pruritic, rash macular and exfoliative rash

[9)] includes cases of myalgia and musculoskeletal pain

[10)] includes cases of oedema peripheral, oedema, generalised oedema, eyelid oedema, periorbital oedema, face oedema and localised oedema

Serious adverse event / deaths / other significant events

Serious Adverse events

Table 27: SAEs Occurring in at Least Two Patients in Either Treatment Arm (Safety Population)

MedDRA Preferred Term, n (%)	Crizotinib N = 151	Alectinib N = 152
Total number of patients with ≥ 1 SAE	44 (29%)	43 (28%)
Pneumonia	4 (3%)	5 (3%)
Pneumonitis	4 (3%)	2 (1%)
Alanine aminotransferase increased	4 (3%)	1 (1%)
Pulmonary embolism	3 (2%)	2 (1%)
Pyrexia	3 (2%)	1 (1%)
Nausea	3 (2%)	0
Dyspnoea	1 (1%)	2 (1%)
Vomiting	2 (1%)	0
Deep vein thrombosis	2 (1%)	0
Confusional state	2 (1%)	1 (1%)
Lung infection	0	3 (2%)
Bronchitis	0	2 (1%)
Urinary tract infection	0	2 (1%)
Pneumothorax	0	2 (1%)
Blood creatinine increased	0	2 (1%)
Acute kidney injury	0	4 (3%)
Anaemia	0	2 (1%)

SAE = serious adverse event.

Note: Investigator text for SAEs was encoded using MedDRA version 19.1. Percentages were based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same SAE in an individual were counted only once.

Deaths

Table 28: Patients with Grade 5 Adverse Events (Safety Population)

Patient ID	Grade 5 AE (MedDRA PT)	Study Day of Onset
Crizotinib		
	Sudden death	86
	Pneumonitis [a]	38
	Cardiac arrest [a]	328
	Cerebral haemorrhage	457
	Necrotising fascitis	196
	Respiratory failure	251
	Dyspnoea	53
Alectinib		
	Acute kidney injury	14
	Blood creatinine increased	448
	Death	24
	Cardiac arrest	22
	Lung infection	13

AE = adverse event; ID = identification; PT = Preferred Term.

[a] Considered treatment-related by the investigator.

Laboratory findings

Table 29: Treatment-emergent Shifts in Key Laboratory Abnormalities that Occurred in > 10% of Patients Treated with alectinib (Safety Population)

Laboratory Parameter	All Grades N=147	Grades 3–4[a] N=147
Chemistry		
Increased blood creatinine[b]	56 (38%)	5 (3.4%)
Increased blood creatine phosphokinase[c]	48 (37%)	4 (3.1%)
Increased aspartate aminotransferase[d]	73 (50%)	9 (6.2%)
Increased blood bilirubin[e]	78 (53%)	8 (5.5%)
Increased alanine aminotransferase	59 (40%)	9 (6.1%)
Increase in alkaline phosphatase	73 (50%)	0
Hematology		
Decreased hemoglobin	91 (62%)	10 (6.8%)

NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Laboratory abnormalities were based on the normal ranges of the NCI CTCAE.

[a] No Grade 5 laboratory abnormalities were reported.

[b] Only patients with creatinine increases based on the Upper Limit of Normal definition (NCI CTCAE grading).

[c] Fourteen patients with missing baseline values in alectinib arm not included; N=129

[d] Two patients with missing baseline values in alectinib arm not included; N=145

[e] One patient with missing baseline value in alectinib arm not included; N=146

Clinically relevant shifts were defined as a shift from NCI CTCAE Grade 0, 1 or 2 at baseline to Grade 3 or 4 post-baseline.

Elevations of CPK occurred in 43% of 362 patients with CPK laboratory data available across clinical trials (NP28761, NP28673, BO28984) with alectinib. The incidence of Grade 3 elevations of CPK was 3.7%.

Haematology

Table 30: Summary of Clinically Relevant Shifts from Baseline in Haematology Safety Parameters (Safety Population)

Hematology Parameters	Crizotinib N=151	Alectinib N=152
Neutrophils - Low	10/148 (7%)	0 (0%)
Lymphocytes - Low	6/148 (4%)	2/146 (1%)
Hemoglobin - Low	1/148 (1%)	10/147 (7%)
Platelets - Low	1/148 (1%)	1/147 (1%)
White blood cell count - Low	1/148 (1%)	0 (0%)

Note: A clinically relevant shift was defined as a shift from Grade 0, 1 or 2 at baseline to Grade 3 or 4 post-baseline, based on the National Cancer Institute Common Terminology Criteria for Adverse Events. Baseline was defined as the patient's last observation prior to initiation of study drug; patients without any post-baseline grades were not reported.

Source: ALEX CSR, CTD Module 5.3.5.1: Output t_lb_shift_HEM_SE

Blood chemistry

Table 31: Summary of Clinically Relevant Shifts from Baseline in Blood Chemistry Safety Parameters

Chemistry Parameters	Crizotinib N=151	Alectinib N=152
SGPT/ALT – High	24/148 (16%)	9/147 (6%)
SGOT/AST – High	17/148 (11%)	9/145 (6%)
Sodium – Low	6/147 (4%)	9/147 (6%)
Bilirubin – High	0 (0%)	8/146 (5%)
Creatinine [a] – High	1/148 (1%)	5/147 (3%)
Creatine kinase – High	2/130 (2%)	4/129 (3%)
Blood glucose – High	3/123 (2%)	3/116 (3%)
Phosphorus – Low	4/144 (3%)	2/143 (1%)
Albumin - Low	5/147 (3%)	0 (0%)
Calcium – Low	2/148 (1%)	0 (0%)
Gamma-glutamyltransferase – High	4/143 (3%)	1/139 (1%)
Magnesium – Low	0 (0%)	1/144 (1%)
Magnesium – High	1/144 (1%)	2/144 (1%)
Potassium – Low	1/148 (1%)	3/147 (2%)
Potassium – High	2/148 (1%)	2/147 (1%)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = upper limit of normal.

Note: A clinically relevant shift was defined as a shift from Grade 0, 1 or 2 at baseline to Grade 3 or 4 post-baseline, based on the National Cancer Institute Common Terminology Criteria for Adverse Events. Baseline was defined as the patient's last observation prior to initiation of study drug; patients without any post-baseline grades were not reported.

[a] Based on abnormality grades that were modified from the standard National Cancer Institute Common Terminology Criteria definitions as follows: Grade 0 abnormality: ≤ ULN; Grade 1 abnormality: ≤ 1.5 × ULN; Grade 2 abnormality: ≤ 3 × ULN; Grade 3 abnormality: ≤ 6 × ULN; and Grade 4 abnormality: > 6 × ULN.

Source: ALEX CSR, CTD Module 5.3.5.1: Outputs t_lb_shift_CHEM_SE and t_lb_shift_creatn_SE

Urinalysis

Two of 134 patients in the alectinib arm and two of 130 patients in the crizotinib arm experienced a clinically relevant shift in urine protein. No clinically relevant shifts were seen for urine albumin or urine creatinine.

Hormone evaluation

In both treatment arms, few male patients experienced abnormalities in FSH, LH, or testosterone concentrations throughout the study. More male patients in the alectinib arm tended to have high FSH and high LH (relative to baseline) as compared to patients in the crizotinib arm where low testosterone tended to be observed.

Vital signs

Electrocardiogram

ECG findings showed post-baseline increases in median values for PR, QT, and QT corrected using Fridericia's formula (QTcF) and a decrease in heart rate in both treatment arms. Few patients 7/144 patients [5%]) had clinically relevant ECG abnormalities post-baseline in the alectinib arm.

Most patients in both treatment arms had a maximum post-baseline QTcF interval of ≤ 450 msec (80% crizotinib vs. 93% alectinib). Moderate (> 480 to ≤ 500 msec) and severe (> 500 msec) QTcF

prolongation was experienced by more patients on crizotinib (3% and 6%, respectively) than alectinib (1% and 0%, respectively). Similarly, absolute changes from baseline in QTcF that were moderate (> 30 to ≤ 60 msec) or severe (> 60 msec) occurred in more patients receiving crizotinib (26% and 10%, respectively) than alectinib (20% and 1%, respectively).

Bradycardia

Cases of bradycardia (8.9%) of Grade 1 or 2 have been reported in patients treated with Alecensa across clinical trials (NP28761, NP28673, BO28984). No patients had events of Grade ≥ 3 severity. There were 66 of 365 patients (18%) treated with Alecensa who had post-dose heart rate values below 50 beats per minutes (bpm). In the phase III clinical trial BO28984 15% of patients treated with Alecensa had post-dose heart rate values below 50 bpm versus 20% of patients treated with crizotinib.

Safety in special populations

Gender

Overall, a comparable proportion of male and female patients in each treatment arm experienced an AE, and the most frequently occurring AEs for male and female patients were consistent with the overall population for the respective treatment arm.

Table 32: Adverse Events in ≥20% of Male and Female Patients in Any Subgroup (Safety Population)

	Crizotinib (N=151)		Alectinib (N=152)	
MedDRA System Organ Class MedDRA Preferred Term	Male (N=64)	Female (N=87)	Male (N=68)	Female (N=84)
Total number of patients with at least one adverse event	59 (92.2%)	87 (100.0%)	65 (95.6%)	82 (97.6%)
Overall total number of events	520	845	503	693
GASTROINTESTINAL DISORDERS				
Total number of patients with at least one adverse event	44 (68.8%)	76 (87.4%)	39 (57.4%)	45 (53.6%)
Total number of events	149	253	78	110
CONSTIPATION	22 (34.4%)	27 (31.0%)	24 (35.3%)	28 (33.3%)
NAUSEA	23 (35.9%)	49 (56.3%)	10 (14.7%)	11 (13.1%)
DIARRHOEA	30 (46.9%)	38 (43.7%)	6 (8.8%)	12 (14.3%)
VOMITING	19 (29.7%)	39 (44.8%)	6 (8.8%)	5 (6.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Total number of patients with at least one adverse event	34 (53.1%)	52 (59.8%)	29 (42.6%)	48 (57.1%)
Total number of events	61	92	55	92
OEDEMA PERIPHERAL	16 (25.0%)	26 (29.9%)	9 (13.2%)	17 (20.2%)
FATIGUE	11 (17.2%)	14 (16.1%)	14 (20.6%)	15 (17.9%)
INVESTIGATIONS				
Total number of patients with at least one adverse event	27 (42.2%)	42 (48.3%)	36 (52.9%)	34 (40.5%)
Total number of events	59	114	99	64
ALANINE AMINOTRANSFERASE INCREASED	14 (21.9%)	31 (35.6%)	12 (17.6%)	11 (13.1%)
ASPARTATE AMINOTRANSFERASE INCREASED	13 (20.3%)	24 (27.6%)	9 (13.2%)	12 (14.3%)
BLOOD BILIRUBIN INCREASED	1 (1.6%)	1 (1.1%)	14 (20.6%)	9 (10.7%)
NERVOUS SYSTEM DISORDERS				
Total number of patients with at least one adverse event	27 (42.2%)	41 (47.1%)	19 (27.9%)	20 (23.8%)
Total number of events	43	76	23	39
DYSGEUSIA	11 (17.2%)	18 (20.7%)	1 (1.5%)	3 (3.6%)
INFECTIONS AND INFESTATIONS				
Total number of patients with at least one adverse event	20 (31.3%)	25 (28.7%)	24 (35.3%)	37 (44.0%)
Total number of events	32	38	38	70
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
Total number of patients with at least one adverse event	19 (29.7%)	23 (26.4%)	25 (36.8%)	30 (35.7%)
Total number of events	23	31	42	68
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Total number of patients with at least one adverse event	22 (34.4%)	23 (26.4%)	19 (27.9%)	29 (34.5%)
Total number of events	32	38	40	55
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Total number of patients with at least one adverse event	12 (18.8%)	26 (29.9%)	15 (22.1%)	26 (31.0%)
Total number of events	15	38	27	41
METABOLISM AND NUTRITION DISORDERS				
Total number of patients with at least one adverse event	12 (18.8%)	23 (26.4%)	16 (23.5%)	19 (22.6%)
Total number of events	23	42	21	27
EYE DISORDERS				
Total number of patients with at least one adverse event	17 (26.6%)	33 (37.9%)	3 (4.4%)	9 (10.7%)
Total number of events	23	39	3	10
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
Total number of patients with at least one adverse event	8 (12.5%)	11 (12.6%)	15 (22.1%)	18 (21.4%)
Total number of events	14	20	18	35
ANAEMIA	3 (4.7%)	4 (4.6%)	13 (19.1%)	17 (20.2%)

Investigator text for AEs encoded using MedDRA version 19.1. 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. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Data cutoff: 09 February 2017.

Age

Table 33: Adverse Events in ≥20% of Patients < 65 or ≥ 65 Years of Age in Any Subgroup (Safety Population)

MedDRA System Organ Class MedDRA Preferred Term	Crizotinib (N=151) < 65 years (N=118)	Crizotinib (N=151) >= 65 years (N=33)	Alectinib (N=152) < 65 years (N=115)	Alectinib (N=152) >= 65 years (N=37)
Total number of patients with at least one adverse event	113 (95.8%)	33 (100.0%)	112 (97.4%)	35 (94.6%)
Overall total number of events	999	366	889	307
GASTROINTESTINAL DISORDERS				
Total number of patients with at least one adverse event	92 (78.0%)	28 (84.8%)	68 (59.1%)	16 (43.2%)
Total number of events	299	103	147	41
CONSTIPATION	33 (28.0%)	16 (48.5%)	41 (35.7%)	11 (29.7%)
NAUSEA	52 (44.1%)	20 (60.6%)	19 (16.5%)	2 (5.4%)
DIARRHOEA	54 (45.8%)	14 (42.4%)	12 (10.4%)	6 (16.2%)
VOMITING	48 (40.7%)	10 (30.3%)	9 (7.8%)	2 (5.4%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Total number of patients with at least one adverse event	64 (54.2%)	22 (66.7%)	56 (48.7%)	21 (56.8%)
Total number of events	104	49	110	37
OEDEMA PERIPHERAL	29 (24.6%)	13 (39.4%)	20 (17.4%)	6 (16.2%)
FATIGUE	16 (13.6%)	9 (27.3%)	20 (17.4%)	9 (24.3%)
INVESTIGATIONS				
Total number of patients with at least one adverse event	52 (44.1%)	17 (51.5%)	50 (43.5%)	20 (54.1%)
Total number of events	119	54	117	46
ALANINE AMINOTRANSFERASE INCREASED	34 (28.8%)	11 (33.3%)	21 (18.3%)	2 (5.4%)
ASPARTATE AMINOTRANSFERASE INCREASED	25 (21.2%)	12 (36.4%)	18 (15.7%)	3 (8.1%)
BLOOD BILIRUBIN INCREASED	1 (0.8%)	1 (3.0%)	15 (13.0%)	8 (21.6%)
NERVOUS SYSTEM DISORDERS				
Total number of patients with at least one adverse event	47 (39.8%)	21 (63.6%)	36 (31.3%)	3 (8.1%)
Total number of events	81	38	58	4
DYSGEUSIA	16 (13.6%)	13 (39.4%)	4 (3.5%)	0
INFECTIONS AND INFESTATIONS				
Total number of patients with at least one adverse event	32 (27.1%)	13 (39.4%)	41 (35.7%)	20 (54.1%)
Total number of events	49	21	71	37
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
Total number of patients with at least one adverse event	32 (27.1%)	10 (30.3%)	42 (36.5%)	13 (35.1%)
Total number of events	42	12	83	27
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Total number of patients with at least one adverse event	35 (29.7%)	10 (30.3%)	31 (27.0%)	17 (45.9%)
Total number of events	55	15	60	35
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Total number of patients with at least one adverse event	33 (28.0%)	5 (15.2%)	33 (28.7%)	8 (21.6%)
Total number of events	47	6	53	15
METABOLISM AND NUTRITION DISORDERS				
Total number of patients with at least one adverse event	24 (20.3%)	11 (33.3%)	24 (20.9%)	11 (29.7%)
Total number of events	43	22	31	17
DECREASED APPETITE	9 (7.6%)	5 (15.2%)	6 (5.2%)	8 (21.6%)
EYE DISORDERS				
Total number of patients with at least one adverse event	38 (32.2%)	12 (36.4%)	9 (7.8%)	3 (8.1%)
Total number of events	48	14	10	3
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
Total number of patients with at least one adverse event	15 (12.7%)	4 (12.1%)	25 (21.7%)	8 (21.6%)
Total number of events	29	5	38	15
ANAEMIA	5 (4.2%)	2 (6.1%)	22 (19.1%)	8 (21.6%)
CARDIAC DISORDERS				
Total number of patients with at least one adverse event	19 (16.1%)	7 (21.2%)	18 (15.7%)	7 (18.9%)
Total number of events	20	9	22	7

Investigator text for AEs encoded using MedDRA version 19.1. 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. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Data cutoff: 09 February 2017.

Race

Table 34: Adverse Events in ≥20% of Asian and Non-Asian Patients in Any Subgroup (Safety Population)

MedDRA System Organ Class MedDRA Preferred Term	Crizotinib (N=151)		Alectinib (N=152)	
	Asian (N=69)	Non-Asian (N=82)	Asian (N=69)	Non-Asian (N=83)
Total number of patients with at least one adverse event	66 (95.7%)	80 (97.6%)	68 (98.6%)	79 (95.2%)
Overall total number of events	593	772	570	626
GASTROINTESTINAL DISORDERS				
Total number of patients with at least one adverse event	56 (81.2%)	64 (78.0%)	47 (68.1%)	37 (44.6%)
Total number of events	182	220	100	88
CONSTIPATION	29 (42.0%)	20 (24.4%)	28 (40.6%)	24 (28.9%)
NAUSEA	29 (42.0%)	43 (52.4%)	7 (10.1%)	14 (16.9%)
DIARRHOEA	27 (39.1%)	41 (50.0%)	10 (14.5%)	8 (9.6%)
VOMITING	33 (47.8%)	25 (30.5%)	7 (10.1%)	4 (4.8%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Total number of patients with at least one adverse event	33 (47.8%)	53 (64.6%)	30 (43.5%)	47 (56.6%)
Total number of events	60	93	56	91
OEDEMA PERIPHERAL	16 (23.2%)	26 (31.7%)	5 (7.2%)	21 (25.3%)
FATIGUE	5 (7.2%)	20 (24.4%)	14 (20.3%)	15 (18.1%)
INVESTIGATIONS				
Total number of patients with at least one adverse event	33 (47.8%)	36 (43.9%)	39 (56.5%)	31 (37.3%)
Total number of events	98	75	96	67
ALANINE AMINOTRANSFERASE INCREASED	26 (37.7%)	19 (23.2%)	15 (21.7%)	8 (9.6%)
ASPARTATE AMINOTRANSFERASE INCREASED	20 (29.0%)	17 (20.7%)	14 (20.3%)	7 (8.4%)
NERVOUS SYSTEM DISORDERS				
Total number of patients with at least one adverse event	31 (44.9%)	37 (45.1%)	18 (26.1%)	21 (25.3%)
Total number of events	50	69	33	29
DYSGEUSIA	9 (13.0%)	20 (24.4%)	2 (2.9%)	2 (2.4%)
INFECTIONS AND INFESTATIONS				
Total number of patients with at least one adverse event	20 (29.0%)	25 (30.5%)	30 (43.5%)	31 (37.3%)
Total number of events	28	42	52	56
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
Total number of patients with at least one adverse event	20 (29.0%)	22 (26.8%)	24 (34.8%)	31 (37.3%)
Total number of events	20	34	47	63
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Total number of patients with at least one adverse event	20 (29.0%)	25 (30.5%)	20 (29.0%)	28 (33.7%)
Total number of events	30	40	42	53
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Total number of patients with at least one adverse event	19 (27.5%)	19 (23.2%)	17 (24.6%)	24 (28.9%)
Total number of events	29	24	35	33
METABOLISM AND NUTRITION DISORDERS				
Total number of patients with at least one adverse event	15 (21.7%)	20 (24.4%)	19 (27.5%)	16 (19.3%)
Total number of events	30	35	28	20
EYE DISORDERS				
Total number of patients with at least one adverse event	21 (30.4%)	29 (35.4%)	4 (5.8%)	8 (9.6%)
Total number of events	26	36	5	8
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
Total number of patients with at least one adverse event	6 (8.7%)	13 (15.9%)	14 (20.3%)	19 (22.9%)
Total number of events	7	27	29	24
ANAEMIA	2 (2.9%)	5 (6.1%)	13 (18.8%)	17 (20.5%)
PSYCHIATRIC DISORDERS				
Total number of patients with at least one adverse event	3 (4.3%)	14 (17.1%)	7 (10.1%)	18 (21.7%)
Total number of events	4	20	7	23

Investigator text for AEs encoded using MedDRA version 19.1. 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. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Data cutoff: 09 February 2017.

Discontinuation due to adverse events

Table 35: AEs Leading to Treatment Discontinuation in at Least Two Patients in Either Treatment Arm (Safety Population)

MedDRA Preferred Term, n (%)	Crizotinib N = 151	Alectinib N = 152
Total number of patients with ≥ 1 AE	19 (13%)	17 (11%)
Alanine aminotransferase increased	8 (5%)	2 (1%)
Aspartate aminotransferase increased	6 (4%)	2 (1%)
Pneumonitis	4 (3%)	1 (1%)
Acute kidney injury	0	3 (2%)
Hyperbilirubinaemia	0	2 (1%)

AE = adverse event.

Note: Investigator text for AEs was encoded using MedDRA version 19.1. Percentages were based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual were counted only once.

Source: ALEX CSR, CTD Module 5.3.5.1: Table 40

Table 36: AEs Leading to Study Drug Interruption in at Least Two Patients in Either Treatment Arm (Safety Population)

MedDRA Preferred Term, n (%)	Crizotinib N = 151	Alectinib N = 152
Total number of patients with ≥ 1 AE	38 (25%)	29 (19%)
Aspartate aminotransferase increased	6 (4%)	3 (2%)
Vomiting	4 (3%)	1 (1%)
Neutropenia	4 (3%)	0
Alanine aminotransferase increased	3 (2%)	4 (3%)
Diarrhoea	3 (2%)	0
Blood creatine phosphokinase increased	2 (1%)	2 (1%)
Electrocardiogram QT prolonged	2 (1%)	0
Nausea	2 (1%)	1 (1%)
Pleural effusion	2 (1%)	0
Pyrexia	2 (1%)	2 (1%)
Pneumonia	0	4 (3%)
Cough	0	2 (1%)
Hyperbilirubinaemia	0	3 (2%)

AE = adverse event.

Note: Investigator text for AEs was encoded using MedDRA version 19.1. Percentages were based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual were counted only once.

Source: ALEX CSR, CTD Module 5.3.5.1: Table 42

Table 37: AEs Leading to Dose Reduction in at Least Two Patients in Either Treatment Arm (Safety Population)

MedDRA Preferred Term, n (%)	Crizotinib N = 151	Alectinib N = 152
Total number of patients with ≥ 1 AE	31 (21%)	24 (16%)
Alanine aminotransferase increased	13 (9%)	3 (2%)
Aspartate aminotransferase increased	9 (6%)	5 (3%)
Nausea	2 (1%)	1 (1%)
Vomiting	2 (1%)	1 (1%)
Electrocardiogram QT prolonged	2 (1%)	0
Asthenia	2 (1%)	0
Bradycardia	2 (1%)	0
Blood creatinine increased	1 (1%)	2 (1%)
Anaemia	0	3 (2%)
Blood bilirubin increased	0	3 (2%)
Hyperbilirubinaemia	0	3 (2%)
Rash	0	2 (1%)
Pneumonia	0	2 (1%)

AE = adverse event.

Note: Investigator text for AEs was encoded using MedDRA version 19.1. Percentages were based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual were counted only once.

Source: ALEX CSR, CTD Module 5.3.5.1: Table 43.

Supportive data

The Phase III **J-ALEX** study (103 patients in alectinib arm and 104 patients in crizotinib arm) was conducted in Japan at the Japanese approved dose of alectinib 300 mg BID which equals half of the recommended global dose i.e. 600 mg BID.

The median duration of follow-up was comparable in both arms (12 months [range: 2-23 months] crizotinib vs. 13 months [range: 4-24 months] alectinib).

Table 38: J-ALEX: Overview of Adverse Events (Safety Population)

	Crizotinib N = 104	Alectinib N = 103
Total number of patients with ≥ 1 AE, n (%)	104 (100%)	100 (97%)
Total number of events, n	1278	590
Total number of deaths due to disease progression, n (%)	2 (2%)	7 (7%)
Total number of patients with ≥ 1, n (%)		
AE with fatal outcome (Grade 5)	0	0
Serious AE	27 (26%)	15 (15%)
Grade 3-4 AE	54 (52%)	27 (26%)
AE leading to withdrawal from treatment	21 (20%)	9 (9%)
AE leading to dose suspension	77 (74%)	30 (29%)

AE = adverse event.

Note: Investigator text for AEs was encoded using the Medical Dictionary for Regulatory Activities version 16.1.

Note: Multiple occurrences of the same AE in one individual were counted only once except for 'Total number of events' row in which multiple occurrences of the same AE were counted separately.

Table 39: J-ALEX: Adverse Events in ≥ 20% of Patients (in Either Treatment Arm) (Safety Population)

MedDRA Preferred Term, n (%)	Crizotinib N = 104	Alectinib N = 103
Nausea	77 (74%)	11 (11%)
Diarrhoea	76 (73%)	9 (9%)
Vomiting	60 (58%)	6 (6%)
Visual impairment	57 (55%)	1 (1%)
Dysgeusia	54 (52%)	19 (18%)
Constipation	46 (44%)	36 (35%)
Alanine aminotransferase increased	33 (32%)	9 (9%)
Aspartate aminotransferase increased	32 (31%)	11 (11%)
Nasopharyngitis	24 (23%)	21 (20%)
Pyrexia	21 (20%)	10 (10%)
Decreased appetite	21 (20%)	1 (1%)

MedDRA = Medical Dictionary for Regulatory Activities.

Note: Investigator text for adverse events was encoded using MedDRA version 16.1.

Note: Multiple occurrences of the same adverse event in one individual were counted only once.

Adverse Events by Severity

Table 40: J-ALEX: Grade ≥ 3 Adverse Events in ≥ 5% of Patients (in Either Treatment Arm) (Safety Population)

MedDRA Preferred Term, n (%)	Crizotinib N = 104	Alectinib N = 103
Total number of patients with ≥ 1 adverse event	54 (52%)	27 (26%)
Neutrophil count decreased	14 (14%)	2 (2%)
Alanine aminotransferase increased	13 (13%)	1 (1%)
Electrocardiogram QT prolonged	7 (7%)	2 (2%)
Hepatic function abnormal	6 (6%)	0
Aspartate aminotransferase increased	5 (5%)	1 (1%)
Blood creatine phosphokinase increased	3 (3%)	5 (5%)
Interstitial lung disease	3 (3%)	5 (5%)

MedDRA = Medical Dictionary for Regulatory Activities.

Note: Investigator text for adverse events was encoded using MedDRA version 16.1.

Note: Multiple occurrences of the same adverse event in one individual were counted only once.

Serious adverse event

Table 41: J-ALEX: SAEs in > 1 Patient (in Either Treatment Arm) (Safety Population)

MedDRA Preferred Term, n (%)	Crizotinib N = 104	Alectinib N = 103
Total number of patients with ≥ 1 SAE	27 (26%)	15 (15%)
Interstitial lung disease	5 (5%)	6 (6%)
Alanine aminotransferase increased	3 (3%)	0
Nausea	3 (3%)	0
Hepatic function abnormal	3 (3%)	0
Aspartate aminotransferase increased	2 (2%)	0
Oesophagitis	2 (2%)	0
Blood creatinine increased	2 (2%)	2 (2%)
Electrocardiogram QT prolonged	2 (2%)	1 (1%)
Pulmonary embolism	2 (2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.

Note: Investigator text for adverse events was encoded using MedDRA version 16.1.

Note: Multiple occurrences of the same adverse event in one individual were counted only once.

Deaths

Either in the J-ALEX study or AF-001JP there were no deaths considered AE related. All deaths were attributed to disease progression.

Other significant events

Table 42: J-ALEX: Adverse Events Leading to Discontinuation of Treatment (Safety Population)

MedDRA Preferred Term, n (%)	Crizotinib N = 104	Alectinib N = 103
Total patients with ≥ 1 adverse event	21 (20%)	9 (9%)
Interstitial lung disease	8 (8%)	8 (8%)
Hepatic function abnormal	5 (5%)	0
Alanine aminotransferase increased	4 (4%)	0
Aspartate aminotransferase increased	1 (1%)	0
Blood bilirubin increased	1 (1%)	0
Electrocardiogram QT prolonged	1 (1%)	0
Bradycardia	1 (1%)	0
Acute myeloid leukaemia	1 (1%)	0
Rash maculo-papular	1 (1%)	0
Enterocolitis	0	1 (1%)

MedDRA = Medical Dictionary for Regulatory Activities.

Note: Investigator text for adverse events was encoded using MedDRA version 16.1.

Note: Multiple occurrences of the same adverse event in one individual were counted only once.

Table 43: J-ALEX: Adverse Events Leading to Dose Interruption in > 1 Patient (in Either Treatment Arm) (Safety Population)

MedDRA Preferred Term, n (%)	Crizotinib N = 104	Alectinib N = 103
Total patients with ≥ 1 adverse event	77 (74%)	30 (29%)
Alanine aminotransferase increased	13 (13%)	1 (1%)
Neutrophil count decreased	13 (13%)	0
Nausea	12 (12%)	0
Aspartate aminotransferase increased	9 (9%)	1 (1%)
Vomiting	9 (9%)	0
Oesophagitis	7 (7%)	0
Electrocardiogram QT prolonged	6 (6%)	1 (1%)
Decreased appetite	6 (6%)	0
Diarrhoea	5 (5%)	1 (1%)
Nasopharyngitis	4 (4%)	1 (1%)
Pneumonia	4 (4%)	0
Pyrexia	4 (4%)	0
Bronchitis	3 (3%)	3 (3%)
Upper respiratory tract infection	3 (3%)	1 (1%)
Malaise	3 (3%)	0
Oedema peripheral	3 (3%)	0
Blood creatine phosphokinase increased	2 (2%)	7 (7%)
White blood cell count decreased	2 (2%)	0
Constipation	2 (2%)	0
Lung infection	2 (2%)	1 (1%)
Sinus bradycardia	2 (2%)	0
Blood creatinine increased	0	2 (2%)
Rash maculo-papular	0	3 (3%)

MedDRA = Medical Dictionary for Regulatory Activities.

Note: Investigator text for adverse events was encoded using MedDRA version 16.1.

Note: Multiple occurrences of the same adverse event in one individual were counted only once.

Post marketing experience

As of April 2017, alectinib 600 mg BID was approved in 38 countries globally for the treatment of patients who have progressed on or are intolerant to crizotinib therapy. As of 29 April 2017, the estimated cumulative market exposure to alectinib is 6275 patients (300 mg BID: Japan, n = 3831; 600 mg BID: US, n = 2238; European Economic Area, n = 47; Rest of World, n = 159) since its International Birth Date of 4 July 2014. The alectinib safety profile in the post-marketing period is consistent with safety data from clinical trials of alectinib.

2.5.1. Discussion on clinical safety

Safety data are available from a total of 303 patients in the ALEX study (N=152 alectinib; N=151 crizotinib).

In terms of exposure, the median duration of treatment was 18 months (range: 0-29 months) in the alectinib arm as compared with 11 month (range: 0-27 months) in the crizotinib arm. The proportion of patients that completed > 12 months of treatment was 66 % and 45 % for alectinib and crizotinib respectively and 49 % and 27 % completed > 18 months respectively. The mean dose intensity was comparable between treatment arms (92% for crizotinib and 96% for alectinib).

The same proportion of patients reported ≥1 AE in the two arms (97 %). Likewise there is a similarity in terms of AEs with fatal outcomes, serious AEs (approximately 29 %) and AES leading to treatment discontinuations (approximately 12 %). However, Grade ≥3 events and AEs leading to drug interruption and dose reductions occurred to a lesser extent in the alectinib arm (41 %, 19 % and 16 % respectively in the alectinib arm vs. 50 %, 25 % and 21 % respectively in the crizotinib arm). The longer duration of alectinib treatment compared to crizotinib should also be taken into account when considering these rates.

With the exception for constipation that was similar between the two arms, rash, arthralgia, myalgia, anaemia and blood bilirubin increased constituted AEs more commonly reported for alectinib whilst GI disorders were more commonly reported in the crizotinib arm.

Grade 5 AEs occurred in seven patients (5%) receiving crizotinib and five patients (3%) receiving alectinib. Narratives have been provided. Two events in the crizotinib arm (pneumonitis and cardiac arrest) and none in the alectinib arm were reported by the investigator as treatment-related.

In general, gender did not substantially influence the type of AEs reported.

Nausea/vomiting, ALAT and ASAT increases were more commonly reported in the younger age-group whilst fatigue, decreased appetite and bilirubin increases were more often reported in the older age-group. However, a firm conclusion is hampered by the small numbers of patients ≥ 65 years enrolled in the ALEX study (N=37 patients ≥65, N=115 <65 in the alectinib arm and similar in the crizotinib arm).

In the ALEX study, about 50 % of the patients were Caucasian and 45 % were Asian. Some differences in the incidence of individual AEs were observed. For alectinib peripheral oedema was reported in a higher proportion (≥ 10% absolute difference) of non-Asian patients whereas constipation, increased AST, and increased ALT were reported in higher proportions of Asian patients. In the crizotinib arm, higher proportions (≥ 10% absolute difference) of non-Asian patients reported nausea, diarrhoea, fatigue, and dysgeusia, whereas vomiting, constipation, and increased ALT were reported in higher proportions of Asian patients. Due to the limited number of patients other than Asians or non-Asians enrolled, no conclusions can be drawn.

Embryo-foetal toxicity is an important potential risk to the use of alectinib as reflected in sections 4.4 and 4.6 of the SmPC. The MAH will implement a targeted questionnaire in the event of a pregnancy occurring during alectinib treatment as a routine pharmacovigilance activity (see RMP).

As also demonstrated in the Japanese J-ALEX study, at the dose of 300 mg BID the safety profile of alectinib appears to compare favourably to that of crizotinib administered at the (EU approved) dose of 250 mg BID. The safety database in this study encompasses 161 alectinib-treated patients.

Consistent with the ALEX study, almost all patients reported at least one AE in both arms. Grade 3/4 events and serious events were more often reported in the crizotinib arm compared to alectinib (52 % and 26 % versus 26 % and 15 % for alectinib). In this study there were no fatal events attributed to AEs in either arm.

Data from the J-ALEX study show that haematological events in general occurred with low frequencies and grade of severity. No clinically relevant differences could be observed between patients with and without prior chemotherapy. There is no indication that the use of alectinib in patients with prior chemotherapy leads to higher incidence of haematological events.

Also AEs leading to withdrawal in the J-ALEX study were more commonly reported in the crizotinib arm compared to alectinib (20 % and 9 % respectively) as were AEs leading to study drug suspension (74 % and 29 % respectively). The most commonly reported AEs (occurring in ≥ 20% of patients) with alectinib were constipation (35%) and nasopharyngitis (20%) while in the crizotinib arm, these were nausea (74%), diarrhoea (73%), vomiting (58%), visual impairment (55%), dysgeusia (52%), constipation (44%), alanine aminotransferase (ALT) increased (32%), aspartate aminotransferase (AST) increased (31%), nasopharyngitis (23%), pyrexia (20%) and decreased appetite (20%). Commonly reported in the alectinib arm were also dysgeusia (18%) and stomatitis (12%).

2.5.2. Conclusions on clinical safety

Overall the safety profile of alectinib in 1st line ALK-positive NSCLC is consistent with the known safety profile in the second line setting. The newly identified ADRs from the safety dataset submitted as part of this application are increased weight, acute kidney injury, dysgeusia and stomatitis.

As demonstrated in the ALEX study, the safety profile of alectinib dosed at 600 mg BID compares overall favourably to that of crizotinib. This is further supported by the same observations in the Japanese J-ALEX.

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 CHMP endorsed the Risk Management Plan version 2.2 with the following content:

Safety concerns

Table 44. Summary of the safety concerns

Summary of safety concerns	
Important identified risks	• Interstitial lung disease/pneumonitis • Hepatoxicity • Photosensitivity • Bradycardia • Severe myalgia and CPK elevations
Important potential risks	• Embryo-fetal toxicity
Missing information	• Treatment in patients with moderate or severe hepatic impairment • Long-term safety

Pharmacovigilance plan

Table 45: 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
			N/A	N/A
Category 3 - Required additional pharmacovigilance activities				
NP29783 The effect of hepatic impairment on the pharmacokinetics of alectinib: a multicenter, open-label study following	*Primary Objective:* To assess the PK of alectinib in subjects with hepatic impairment and in matched healthy subjects after a single oral	Treatment of patients with moderate and severe hepatic impairment	1. Protocol submission	December 2015
			2. Study Start	December 2015
			3. Study Finish	28 February 2017
			4. Final report	anticipated Q3, 2017

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
single oral dosing of alectinib to subjects with hepatic impairment and matched healthy subjects with normal hepatic function. Ongoing	dose. *Secondary Objective:* To assess the PK of the major active metabolite of alectinib, M4, and the combined exposure of alectinib and M4 in subjects with hepatic impairment and in matched healthy subjects after a single oral dose. To investigate safety and tolerability of alectinib in subjects with hepatic impairment and in matched healthy subjects. *Exploratory Objective:* To evaluate the relationship, if any, between measures of hepatic impairment			(submission of report: April 2018)

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
	(e.g., Child-Pugh Scores, NCI Criteria for hepatic impairment categories, albumin concentration, etc.) and PK parameters for alectinib and/or M4, as appropriate.			
Category 3 Non-interventional PASS Study Alectinib survey to prescribers: effectiveness measure to investigate the correct implementation of alectinib label guidance by prescribers. Planned	The main objective of the survey is to evaluate the effectiveness of Alecensa's risk minimisation activities of the important identified risks as per label by investigating its correct implementation among HCPs.	Effectiveness measures of the following important identified risks: • Interstitial Lung Disease (ILD)/Pneumonitis • Hepatotoxicity • Photosensitivity • Bradycardia • Severe myalgia and CPK elevations.	Anticipated study start	approximately 18 months after receipt of 1L approval in the EEA
			Anticipated study completion	approximately 24 months after receipt of 1L approval in the EEA
			Estimated submission of final analyses	approximately 12 months after study completion, the results and any proposed actions will be provided

Risk minimisation measures

Table 46. Summary table of pharmacovigilance activities and risk minimisation activities

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Interstitial Lung Disease (ILD)/Pneumonitis	**Routine risk minimisation measures:** *Routine risk communication:* SmPC Section 4.2 Posology and Method of Administration, Special Populations SmPC Section 4.4 Special Warnings and Precautions for Use SmPC Section 4.8 Undesirable Effects, Description of Selected Adverse Reactions Alectinib is a prescription only medicine. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Non-interventional PASS: a survey to prescribers
Hepatotoxicity	**Routine risk minimisation measures:** *Routine risk communication:* SmPC Section 4.2 Posology and Method of Administration, Special Populations SmPC Section 4.4 Special Warnings and Precautions for Use SmPC Section 4.8 Undesirable Effects, Description of Selected Adverse Reactions Alectinib is a prescription only medicine. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Non-interventional PASS: a survey to prescribers
Photosensitivity	**Routine risk minimisation measures:** *Routine risk communication:* SmPC Section 4.4 Special Warnings and Precautions for Use Alectinib is a prescription only	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Non-interventional PASS: a survey to

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	medicine. **Additional risk minimisation measures:** None	prescribers
Bradycardia	**Routine risk minimisation measures:** *Routine risk communication:* SmPC Section 4.2 Posology and Method of Administration, Special Populations SmPC Section 4.4 Special Warnings and Precautions for Use SmPC Section 4.8 Undesirable Effects, Description of Selected Adverse Reactions Alectinib is a prescription only medicine. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Non-interventional PASS: a survey to prescribers
Severe myalgia and CPK elevations	**Routine risk minimisation measures:** *Routine risk communication:* SmPC Section 4.2 Posology and Method of Administration, Special Populations SmPC Section 4.4 Special Warnings and Precautions for Use SmPC Section 4.8 Undesirable Effects, Description of Selected Adverse Reactions Alectinib is a prescription only medicine. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Non-interventional PASS: a survey to prescribers
Embryo-fetal toxicity	**Routine risk communication:** Section 4.6 of the proposed alectinib EU SmPC includes	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. The

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	guidance to avoid exposure **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.4 Special Warnings and Precautions for Use **Other risk minimisation measures beyond the Product Information:** None.	routine activities include guided questionnaire for cases of pregnancy occurring during alectinib treatment **Additional pharmacovigilance activities:** None
Treatment in patients with moderate or severe hepatic impairment	**Routine risk minimisation measures:** *Routine risk communication:* SmPC Section 4.2 Posology and Method of Administration, Special Populations SmPC Section 5.2 Pharmacokinetic Properties; Pharmacokinetics in Special Populations Alectinib is a prescription only medicine. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study NP29783
Long-term safety	**Routine risk minimisation measures:** Continued clinical trial monitoring. *Routine risk communication:* None **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection[1]:** None **Additional pharmacovigilance activities:** None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, Annex II has been updated to reflect that the specific obligation to submit the results of the Phase III study ALEX has been submitted.

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:

- No significant changes impacting the readability of the package leaflet are made. The new additions follow the same structure and use similar descriptions and terminology as used in the approved package leaflet.
- The target group of users will be similar between the approved indication (ALKpositive advanced NSCLC previously treated with crizotinib) and the new indication (first-line treatment of advanced ALK-positive NSCLC), with no significant age difference.
- The posology proposed in this application is the same as the currently approved indication in ALK-positive NSCLC patients previously treated with crizotinib.

2.8. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Alecensa (alectinib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

NSCLC is the leading cause of cancer-related mortality worldwide and represents a major health problem. There are approximately 449,000 cases and 388,000 deaths per year in the European Union (EU) [GLOBOCAN 2012]. The expected 5 year survival rate for all lung cancer patients in the US is only 18% [Siegel et al 2016].

Approximately 5% of NSCLC cases have been shown to harbour the EML4 ALK fusion gene [Barlesi et al 2016] as a result of a chromosomal inversion at 2p21 and 2p23 [Choi et al 2010, Ou et al 2012]. The resulting ALK fusion protein results in activation and dysregulation of the gene's expression and signalling, which can contribute to increased cell proliferation and survival in tumours expressing these genes. Patients with 'ALK positive' tumours tend to have specific clinical features, including never or light smoking history, high frequencies in females, younger age, adenocarcinoma histology, and are sensitive to therapy with ALK inhibitors [Gridelli et al 2014]. ALK positive NSCLC patients can develop resistance and progression of disease particularly in the CNS resulting in poor prognosis.

3.1.2. Available therapies and unmet medical need

Crizotinib is the current standard of care, and chemotherapy is also available as a first line treatment option for ALK positive NSCLC [ESMO guidelines 2016 and NCCN guidelines 2016]. Crizotinib is the only EU approved ALK inhibitor for the first line treatment of ALK positive NSCLC. Although substantial benefit has been observed with crizotinib therapy, relapse remains the norm as on average patients progress within a year (median PFS = 10.9 months); survival after relapse is poor [Solomon B et al 2014]. The three main reasons for crizotinib treatment failure are: development of resistant mutations [Doebele et al 2012, Katayama et al 2011], activation of alternative pathways, e.g., epidermal growth factor receptor [Doebele et al 2012, Katayama et al 2011, Kim et al 2013], and CNS relapse [Costa et al 2011, Chun et al 2012, Weickhardt et al 2012]. The CNS is the primary site of progression in up to 46% of patients with ALK positive NSCLC treated with crizotinib [Costa et al 2011, Chun et al 2012, Weickhardt et al 2012].

3.1.3. Main clinical studies

In the initial variation application, data from the ongoing Japanese Phase III J-ALEX study and from the Phase I/II AF-001JP study were submitted. However, in response to the request for supplementary information, the MAH has provided data from the primary analysis from the ALEX study (specific obligation), an ongoing, global, randomized (1:1), multicentre Phase III open-label study investigating the efficacy and safety of alectinib 600 mg BID compared with crizotinib 250 mg BID in patients who are treatment-naïve with advanced or recurrent or metastatic (Stage IV) ALK-positive NSCLC. A total of 303 patients were enrolled and randomised to either alectinib 600 mg BID (N=152) or crizotinib (N=151). The posologies are according to their respective label (Alecensa SmPC and Xalkori SmPC).

As a consequence, the MAH requested a conversion of conditional to full marketing authorization within this procedure.

3.2. Favourable effects

The ALEX study met its primary endpoint of PFS as assessed by investigator, with a risk reduction for disease progression or death of 53% compared with crizotinib [HR 0.47 (95% confidence interval [CI]: 0.34-0.65), stratified log-rank p < 0.0001]. The estimated median PFS was 11 months in the crizotinib arm whilst not yet reached in the alectinib arm. The sensitivity analyses performed on PFS support the result in the primary analysis and the treatment effect was consistent across the majority of pre-specified subgroups albeit the limited number of patients in some of them is noted.

Results from the secondary endpoint IRC-assessed PFS were consistent with those of the investigator-assessed PFS with HR 0.50 (95% CI: 0.36-0.70; stratified log-rank p < 0.0001). The median PFS was 10 months in the crizotinib arm and approximately 26 months in the alectinib arm.

Furthermore, alectinib decreased the risk of CNS progression without prior non-CNS progression compared with crizotinib (HR 0.16; 95% CI 0.10-0.28, p < 0.0001). In patients with measurable and non-measurable CNS lesions at baseline (assessed by IRC), more patients in the alectinib arm achieved a CNS response (59%) compared with crizotinib (26%) with 45 % and 9 % complete responses respectively. In the subgroup of patients with baseline measurable CNS lesions, ORR was observed in 81% and 50% respectively with 38 % complete responses in the alectinib arm as compared to 5 % in the crizotinib arm.

Among responders with both measurable and non-measurable CNS lesions at baseline, the median CNS DOR had not yet been reached in the alectinib arm and was about 4 months in the crizotinib arm.

In the subgroup of responders with measurable CNS lesions, the median CNS DOR in responders was 17 months in the alectinib arm and about 6 months in the crizotinib arm.

In terms of overall survival data is as expected, immature with 27% of patients in the crizotinib arm and 23% of patients in the alectinib arm had died at the time of data cut-off. The MAH is recommended to submit the final OS analysis for the ALEX study.

OS was not formally tested for statistical significance (HR 0.76 [95% CI: 0.48, 1.20]) as the previous key secondary endpoint of investigator-assessed ORR in the pre-specified hierarchy was not statistically significant.

In terms of HRQoL/PRO results, baseline compliance for both treatment arms was poor (~65 % completing their baseline assessment). Data are suggestive of increased tolerability for alectinib compared to crizotinib including commonly reported treatment-related symptoms (e.g. GI-related) although the open-label design should be taken into consideration.

Data from the crizotinib-comparative J-ALEX and the Phase I/II AF-001JP studies (Japanese patients dosed at 300 mg BID) supports the findings in the ALEX study.

3.3. Uncertainties and limitations about favourable effects

N/A

3.4. Unfavourable effects

Safety data are available from a total of 303 patients in the ALEX study (N=152 alectinib; N=151 crizotinib).

The same proportion of patients reported ≥ 1 AE in the alectinib and crizotinib arms (97 %). Likewise there is a similarity in terms of AEs with fatal outcomes, serious AEs (approximately 29 %) and AES leading to treatment discontinuations (approximately 12 %).

However, Grade ≥3 AEs and AEs leading to drug interruption and dose reductions occurred to a lesser extent in the alectinib arm (41 %, 19 % and 16 % respectively in the alectinib arm vs. 50 %, 25 % and 21 % respectively in the crizotinib arm). The longer duration of alectinib treatment compared to crizotinib should also be taken into account when considering these rates.

With the exception for constipation that was similar between the two arms, rash, arthralgia, myalgia, anaemia and blood bilirubin increased constituted AEs more commonly reported for alectinib whilst GI disorders were more commonly reported in the crizotinib arm.

Grade 5 AEs occurred in seven patients (5%) receiving crizotinib and five patients (3%) receiving alectinib.

The most common ADRs reported with alectinib in the ALEX trial are: constipation (34%), myalgia (23%), oedema (22%), increased bilirubin (21%) and anaemia (20%).

The most common grade 3/4 ADRs reported with alectinib in the ALEX trial are: Increased AST (5.3%), increased ALT (4.6%), anaemia (4.6%) and increased bilirubin (3.3%).

3.5. Uncertainties and limitations about unfavourable effects

Data on long-term safety is missing as also reflected in the RMP.

3.6. Effects Table

Table 447: Effects Table for alectinib as 1st line treatment in ALK-positive NSCLC (ALEX, data cut-off for the primary analysis: 09 February 2017).

Effect	Short Description	Unit	Treatment alectinib 600 mg BID N=152	Control Crizotinib 250 mg BID N=151	Uncertainties / Strength of evidence	References
Favourable Effects						
Primary endpoint						
PFS INV	median	Mths	NE 95% CI (17.7, NE)	11 95% CI (9.1, 13.1)	• ~54 % event rate • HR 0.47 (95% CI; 0.34, 0.65) P=<0.0001	
1-y event free rate		%	68 95% CI (61.0%, 75.9%)	49 95% CI (40.4%, 56.9%)		
Key Secondary endpoints						
PFS IRC	median	Mths	26 95% CI (19.9, NE)	10 95% CI (7.7, 14.6)	• HR 0.50 (95% CI; 0.36, 0.70) P=<0.0001	
1-y event free rate		%	66.5 95% CI (59.0%, 74.1%)	46 95% CI (37.7, 54.5%)		
Time to CNS progress (IRC) 1-y cum inc rate of CNS progress	Patients with events	% %	12 9 95% CI (5.4%, 14.7%)	45 41 95% CI (33.2%, 49.4%)	• HR 0.16 (95% CI; 0.10,0.28) P=<0.0001	
OS	median	Mths	NE	NE	• Data immature, event rate ~25 % • HR 0.76 (95% CI; 0.48,1.20)	
Unfavourable Effects						
AE grade ≥3		%	41	50		
SAE		%	28	29		
Number of AE with fatal outcome		%	3	5		
AEs reported in at least 10% of patients in either arm (safety population)						
Nausea Grade ≥3		%	14 1	48 3		
Diarrhoea Grade ≥3		%	12 0	45 2		
Vomiting Grade ≥3		%	7 0	38 3		
Constipation Grade ≥3		%	34 0	33 0		
ALAT/ASAT Grade ≥3		%	15/14 5/5	30/25 15/11		
Anaemia Grade ≥3		%	20 5	5 1		
Myalgia Grade ≥3		%	16 0	2 0		
Bilirubin increased Grade ≥3		%	15 2	1 0		
Rash Grade ≥3		%	11 1	9 0		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The data available from the primary analysis of the global ALEX study using the EU-approved alectinib dose of 600 mg BID, showed superiority of alectinib over crizotinib in the 1st line treatment-naïve patients with advanced ALK-positive NSCLC. The treatment effect of alectinib on CNS metastases is compelling and of high clinical relevance.

It is recognised that the safety results from the primary analysis of the ALEX study are essentially consistent with the known safety profile of alectinib. Four new ADRs have been identified based on the new data submitted (stomatitis, dysgeusia, acute kidney injury and increased weight).

Lower proportions of AEs that were treatment-related, Grade ≥3 in severity and that led to dose reduction or interruption were reported for alectinib as compared to crizotinib. The longer treatment duration for alectinib should also be taken into account. From a safety perspective and as demonstrated in the ALEX study, the safety profile of alectinib dosed at 600 mg BID compares overall favourably to that of crizotinib.

3.7.2. Balance of benefits and risks

The data from the primary analysis of the ALEX study showed superiority of alectinib over crizotinib in treatment-naïve patients with advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC in terms of progression-free survival and lower toxicity despite the longer exposure.

The indication wording states that alectinib is indicated in patients with advanced disease which in clinical practice is equivalent to patients with either locally advanced disease not amenable for surgery or patients with metastatic (Stage IV) disease. The wording is from a clinical perspective considered appropriate.

3.7.3. Additional considerations on the benefit-risk balance

A conditional marketing authorisation was granted for alectinib on 16 February 2017 (EMEA/H/C/4164) based on data from two Phase I/II studies (studies NP28673 and NP28761) evaluating alectinib in ALK-positive NSCLC patients who had progressed on crizotinib. The specific obligation linked to the CMA was the submission of the ALEX CSR. As data from the primary analysis of the ALEX study have now been submitted in the context of this variation application, the MAH is requesting the granting of a marketing authorisation no longer subject to specific obligations as the specific obligation is considered fulfilled. The data from this analysis confirms a positive B/R balance for alectinib in the sought indication and constitute a comprehensive data package supporting granting of a marketing authorisation no longer subject to specific obligations for alectinib.

3.8. Conclusions

The overall B/R of Alecensa is positive.

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 and IIIB

Extension of Indication for Alecensa (alectinib) to first line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) including final data report of study BO28984 object of the SOB in the annex II; as a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC and Annex II are updated. The Package Leaflet and the RMP are updated in accordance.

In addition, the CHMP, having considered the application as set out in the appended assessment report and on the basis of the evidence of compliance with the specific obligations submitted by the marketing authorisation holder, is of the opinion that the risk-benefit balance of the above mentioned medicinal product remains favourable. As all specific obligations laid down in Annex II have been fulfilled, pursuant to Article 7 of Regulation (EC) No 507/2006, the CHMP recommends by consensus the granting of a Marketing Authorisation in accordance with Article 14(1) of Regulation (EC) No 726/2004 for the above mentioned medicinal product.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

The CHMP is of the opinion that the following obligation has been fulfilled, and therefore recommends its deletion from the Annex II:

Description	Due date
In order to further confirm the efficacy and safety of alectinib in the treatment of patients with ALK-positive NSCLC, the MAH should submit the clinical study report of the phase III study ALEX comparing alectinib versus crizotinib in treatment naïve patients with ALK-positive NSCLC.	30 April 2018

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication for Alecensa (alectinib) to first line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) including final data report of study BO28984 object of the SOB in the annex II; as a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC and Annex II are updated. The Package Leaflet and the RMP are updated in accordance.

In addition, the CHMP, having considered the application as set out in the appended assessment report and on the basis of the evidence of compliance with the specific obligations submitted by the marketing authorisation holder, is of the opinion that the risk-benefit balance of the above mentioned

medicinal product remains favourable. As all specific obligations laid down in Annex II have been fulfilled, pursuant to Article 7 of Regulation (EC) No 507/2006, the CHMP recommends by consensus the granting of a Marketing Authorisation in accordance with Article 14(1) of Regulation (EC) No 726/2004 for the above mentioned medicinal product.

Summary

Please refer to the Scientific Discussion Alecensa H-4164-II-01.

Attachments

1. Product information (changes highlighted) as adopted by the CHMP on 12 October 2017