NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Alecensa® (alectinib) 150 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 161.3 mg alectinib hydrochloride equivalent to 150 mg alectinib.

Excipients with known effect
Each capsule contains 33.7 mg lactose monohydrate and 6 mg sodium (as sodium lauryl sulfate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule

White hard capsule of 19.2 mm length with “ALE” printed in black ink on the cap and “150 mg” printed in black ink on the body.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adjuvant Treatment of Resected Non-Small Cell Lung Cancer

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

Treatment of Locally Advanced or Metastatic NSCLC

Alecensa is indicated for the treatment of adult patients with ALK-positive, locally advanced or metastatic NSCLC.

4.2 Dose and method of administration

A validated ALK assay is required for the selection of ALK-positive NSCLC patients. ALK positive NSCLC status should be established prior to initiation of Alecensa therapy.

Dose

The recommended dose of Alecensa is 600 mg (four 150 mg capsules) given orally twice daily with food (total daily dose of 1200 mg).

Patients with underlying severe hepatic impairment should receive a dose of 450 mg (three 150 mg capsules) given orally twice daily with food (total daily dose of 900 mg).

Duration of treatment

Adjuvant treatment of resected NSCLC

It is recommended that patients are treated with Alecensa until disease recurrence, unmanageable toxicity or for 2 years.

Treatment of locally advanced or metastatic NSCLC

It is recommended that patients are treated with Alecensa until disease progression or unmanageable toxicity.

Delayed or missed doses

Advise patients that if a dose of Alecensa is missed, or if the patient vomits after taking a dose of Alecensa, patients should be advised not to take an extra dose, but to take the next dose at the regular time.

Dose modifications

Management of adverse events may require temporary interruption, dose reduction or discontinuation of treatment with Alecensa. The dose of Alecensa should be reduced in steps of 150 mg twice daily based on tolerability (see Table 1). Dose modification guidelines for specific adverse events are provided in Table 2 (see also section 4.4). Alecensa treatment should be permanently discontinued if patients are unable to tolerate the 300 mg twice daily dose.

Table 1: Alecensa general dose reduction schedule

Dose event	**Change dose to**
Dose	600 mg twice daily
First dose reduction	450 mg twice daily
Second dose reduction	300 mg twice daily

Table 2: Dose modification guidelines for specific adverse events (see also section 4.4)

Grade	**Alecensa Treatment**
Interstitial Lung Disease (ILD)/ Pneumonitis (all Grades)	Immediately interrupt and permanently discontinue if no other potential causes of ILD/pneumonitis have been identified.

Grade	Alecensa Treatment
ALT or AST elevation of > 5 times ULN with total bilirubin ≤ 2 times ULN	Temporarily withhold until recovery to baseline or (≤ 3 times ULN), then resume at reduced dose (see Table 1).
ALT or AST elevation of > 3 times ULN with total bilirubin elevation > 2 times ULN in the absence of cholestasis or haemolysis	Permanently discontinue Alecensa.
Bradycardia[a] Grade 2 or 3 (symptomatic, may be severe and medically significant, medical intervention indicated)	Temporarily withhold until recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm. Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume at reduced dose (see Table 1) upon recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm.
Bradycardia[a] Grade 4 (life-threatening consequences, urgent intervention indicated)	Permanently discontinue if no contributing concomitant medication is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at reduced dose (see Table 1) upon recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm, with frequent monitoring as clinically indicated. Permanently discontinue in case of recurrence.
CPK elevation > 5 times ULN	Temporarily withhold until recovery to baseline or to ≤ 2.5 times ULN, then resume at same dose.
CPK elevation > 10 times ULN or second occurrence of CPK elevation > 5 times ULN	Temporarily withhold until recovery to baseline or to ≤ 2.5 times ULN, then resume at reduced dose as per Table 1.
Haemolytic anaemia with haemoglobin of < 100 g/L (Grade ≥ 2)	Temporarily withhold until resolution, resume at reduced dose (see Table 1) or permanently discontinue.

ILD=interstitial lung disease; ALT=alanine transaminase; AST=aspartate transaminase; ULN=upper limit of normal; CPK=creatine phosphokinase

[a] Bradycardia=heart rate less than 60 beats per minute (bpm)

Special populations

Elderly (≥ 65 years)

No dose adjustment of Alecensa is required in patients aged 65 years and older.
Age does not have an effect on Alecensa exposure (see section 5.2). However, clinical studies of Alecensa did not include sufficient number of subjects aged 65 and older to determine whether they respond differently from younger subjects.

Renal Impairment

No dose adjustment is required in patients with renal impairment (see section 5.2).

Hepatic Impairment

No dose adjustment is required in patients with underlying mild or moderate hepatic impairment. Patients with underlying severe hepatic impairment should receive a dose of 450 mg given orally twice daily (total daily dose of 900 mg) (see section 5.2).

Paediatric population

The safety and efficacy of Alecensa in children and adolescents below 18 years of age have not been established.

Method of administration

Alecensa is for oral use. The hard capsules should be swallowed whole and must not be opened or dissolved. They must be taken with food.

4.3 Contraindications

Alecensa is contraindicated in patients with a known hypersensitivity to alectinib or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Interstitial Lung Disease (ILD)/Pneumonitis

Cases of severe ILD/pneumonitis have been reported in clinical trials with Alecensa (see section 4.8*)*. Patients should be monitored for pulmonary symptoms indicative of pneumonitis.

Promptly investigate worsening of respiratory symptoms indicative of ILD/pneumonitis (e.g. dyspnoea, cough and fever) in any patient taking Alecensa. Immediately withhold treatment with Alecensa in patients diagnosed with ILD/pneumonitis and permanently discontinue it if no other potential causes of ILD/pneumonitis are identified (see section 4.2).

Hepatotoxicity

Elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) greater than 5 times the upper limit of normal (ULN) as well as bilirubin elevations of more than 3 times the ULN occurred in patients in clinical trials with Alecensa (see section 4.8*).* The majority of these events occurred during the first 3 months of treatment. In Alecensa clinical trials, it was reported that three patients with Grade 3–4 ALT/AST elevations had drug-induced liver injury. Concurrent elevations in ALT or AST greater than or equal to three times the ULN and total bilirubin greater than or equal to two times the ULN, with normal alkaline phosphatase occurred in 1 patient treated in Alecensa clinical trials.

Test for liver function (including ALT, AST, and total bilirubin) at baseline and then every 2 weeks during the first 3 months of treatment. Test periodically during treatment thereafter, with more frequent testing in patients who develop transaminase and bilirubin elevations. Based on the severity of the adverse drug reaction, withhold Alecensa and resume at a reduced dose, or permanently discontinue Alecensa as described in Table 2 (see section 4.2).

Bradycardia

Symptomatic bradycardia can occur with Alecensa (see section 4.8). Heart rate and blood pressure should be monitored regularly. No dose modification is required for asymptomatic bradycardia (see section 4.2). If patients experience symptomatic bradycardia or life-threatening events, concomitant medications known to cause bradycardia, as well as anti-hypertensive medications should be evaluated and Alecensa treatment should be adjusted as described in Table 2 (see section 4.2).

Severe Myalgia and Creatine Phosphokinase (CPK) Elevation

Myalgia/musculoskeletal pain have been reported in patients in clinical trials with Alecensa, including Grade 3 events.

Elevations of CPK occurred in clinical trials with Alecensa, including Grade 3 events. Median time to Grade ≥ 3 CPK elevation was 15 days across clinical trials (see section 4.8).

Advise patients to report any unexplained muscle pain, tenderness, or weakness. Assess CPK levels every fortnight for the first month of treatment and as clinically indicated in patients reporting symptoms. Based on the severity of the CPK elevation, withhold Alecensa, then resume or reduce dose (see section 4.2).

Haemolytic anaemia
Haemolytic anaemia has been reported with Alecensa (see section 5.1 and 4.8). If haemoglobin concentration is below 100 g/L and haemolytic anaemia is suspected, withhold Alecensa and initiate appropriate laboratory testing. If haemolytic anaemia is confirmed, resume at a reduced dose upon resolution or permanently discontinue Alecensa *(*see section 4.2).

Photosensitivity

Photosensitivity to sunlight and/or sunburn have been reported with Alecensa administration (see section 4.8). Study participants were advised to avoid sun exposure and to use broad-spectrum sunscreen. All events were Grade 1 or 2 severity except for one non-serious Grade 3 event.

Advise patients that they should avoid prolonged sun exposure and use a broad-spectrum Ultraviolet A (UVA)/Ultraviolet B (UVB) sunscreen and lip balm (both SPF ≥50) whilst taking Alecensa and for at least 7 days after discontinuation.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on alectinib

CYP3A inducers

Co-administration of multiple oral doses of 600 mg rifampicin once daily, a strong cytochrome p450 (CYP) isozyme CYP3A inducer, with a single oral dose of 600 mg alectinib exhibited a minor effect on combined exposure of alectinib and M4 (geometric mean ratio with/without rifampicin [90% confidence interval]: C_{max} 0.96 [0.88 – 1.05], AUC_{inf} 0.82 [0.74 – 0.90]). Therefore, no dose adjustments are required when Alecensa is co-administered with CYP3A inducers.

CYP3A inhibitors

Co-administration of multiple oral doses of 400 mg posaconazole twice daily, a strong CYP3A inhibitor, with a single oral dose of 300 mg alectinib had a minor effect on combined exposure of alectinib and M4 (geometric mean ratio with/without posaconazole [90% confidence interval]: C_{max} 0.93 [0.81 – 1.08], AUC_{inf} 1.36 [1.24 – 1.49]). Therefore, no dose adjustments are required when Alecensa is co-administered with CYP3A inhibitors.

Medicinal products that increase gastric pH

Although the aqueous solubility of alectinib *in vitro* is pH dependent, a dedicated clinical drug-drug interaction study with 40 mg esomeprazole once daily, a proton pump inhibitor, demonstrated no clinically relevant effect on the combined exposure of alectinib and M4. Therefore, no dose adjustments are required when Alecensa is co-administered with proton pump inhibitors or other drugs which raise gastric pH (e.g. H2 receptor antagonists or antacids).

Effect of transporters on alectinib disposition

Based on *in vitro* data, alectinib is not a substrate of P-glycoprotein (P-gp). Alectinib and M4 are not substrates of breast cancer resistance protein (BCRP) or organic anion-transporting polypeptide (OATP) 1B1/B3. In contrast, M4 is a substrate of P-gp. Alectinib inhibits P-gp, and therefore, it is not expected that co-medication with P-gp inhibitors has a relevant effect on M4 exposure.

Effects of alectinib on other medicines

CYP substrates

In vitro studies suggest that alectinib and M4 do not inhibit CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6. No clinically meaningful effect on the exposure of midazolam (a sensitive CYP3A substrate) or repaglinide (a sensitive CYP2C8 substrate) is expected following co-administration with Alecensa. No dose adjustment is required for co-administered CYP3A substrates.

P-gp and BCRP substrates

In vitro studies suggest that alectinib and M4 inhibit P-gp and BCRP. Therefore, alectinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp or BCRP transporters (the increase in exposure is not expected to be more than 2-fold). Appropriate monitoring is recommended when Alecensa is co-administered with P-gp or BCRP substrates with narrow therapeutic index (e.g. digoxin, dabigatran, methotrexate).

Other transporters

Alectinib did not inhibit OATP1B1, OATP1B3, OAT1, OAT3, or OCT2 transport activity *in vitro*.

4.6 Fertility, pregnancy and lactation

Contraception in males and females

Alecensa may cause fetal harm when administered to a pregnant woman (see section 5.3). Advise females of reproductive potential to avoid pregnancy by using highly effective contraception during treatment with Alecensa and for at least 5 weeks after the final dose.

Based on genotoxicity findings (see section 5.3), advise males with female partners of reproductive potential to use highly effective contraception during treatment with Alecensa and for 3 months following the final dose.

Pregnancy (Category D)

Based on animal studies and its mechanism of action, Alecensa may cause fetal harm if taken during pregnancy (see section 5.3). No clinical studies of Alecensa in pregnant women have been performed.

Female patients who become pregnant while taking Alecensa or during the 5 weeks following the last dose of Alecensa must contact their doctor and should be advised of the potential harm to the fetus. Women who are partners of male patients receiving Alecensa, who become pregnant whilst their partner is taking Alecensa, or during the 3 months following the last dose of Alecensa, must contact their doctor and should be advised of the potential harm to the fetus.

The use of Alecensa during labour and delivery has not been established.

Breastfeeding

There are no data on the presence of alectinib or its metabolites in human milk, the effects of alectinib on the breastfed infant, or its effects on milk production. Because of the potential for serious adverse reactions from alectinib in breastfed infants, advise a lactating woman not to breastfeed during treatment with Alecensa and for 1 week after the final dose.

Fertility

No fertility-specific studies of alectinib in animals have been performed. No adverse effects on male and female reproductive organs were observed in general toxicology studies (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies of the effects on the ability to drive and to use machines have been performed.

Alecensa has minor influence on the ability to drive and use machines. Caution should be exercised when driving or operating machines as patients may experience symptomatic bradycardia (e.g. syncope, dizziness, hypotension) or vision disorders while taking Alecensa (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety data described below reflect exposure to Alecensa in 533 patients with resected (n=128) or metastatic (n=405) ALK-positive NSCLC. These patients received Alecensa at the recommended dose of 600 mg twice daily. In the metastatic NSCLC phase II clinical trials (NP28761 and NP28673), 253 patients received Alecensa; the median duration of exposure was 11.2 months. In the metastatic NSCLC phase III clinical trial ALINA (BO28984), 152 patients received Alecensa; the median duration of exposure was 28.1 months. In the phase III clinical trial for adjuvant treatment of resected NSCLC (BO40336), 128 patients received Alecensa; the median duration of exposure was 23.9 months.

Across clinical trials, the most common (≥ 20%) adverse drug reactions (ADRs) were constipation (38.6%); myalgia (34.9% including myalgia, arthralgia and musculoskeletal pain), oedema (28.5% including peripheral, generalised, eyelid, periorbital, face, localized oedema and peripheral, face, lip, joint and eyelid swelling); increased bilirubin (25.1% including increased blood bilirubin, hyperbilirubinemia, increased bilirubin conjugated and increased bilirubin unconjugated), increased AST (22.7%), anaemia (22.3%, including anaemia, normochromic normocytic anaemia, haemoglobin decreased and cases indicative of haemolytic anemia), increased ALT (20.1%) and rash (20.1%, including rash, rash

maculopapular, dermatitis acneiform, erythema, rash generalised, rash papular, rash pruritic, rash macular, exfoliative rash and rash erythematous).

Adjuvant treatment of resected ALK-Positive NSCLC

The safety of Alecensa was evaluated in ALINA, a multi-centre, open-label, randomised trial for the adjuvant treatment of patients with resected ALK-positive NSCLC (see section 5.1). At the time of disease-free survival (DFS) analysis, the median duration of exposure was 23.9 months for Alecensa and 2.1 months for platinum-based chemotherapy.

Serious adverse reactions occurred in 13% of patients treated with Alecensa; the most frequent serious adverse reaction was pneumonitis (0.8%). Adverse reactions that led to treatment discontinuation of Alecensa occurred in 5.5% of patients; the most frequent adverse reaction (⩾ 2%) that led to treatment discontinuation was pneumonitis (2.3%). Adverse reactions that led to dose reductions and interruptions occurred in 26% and 27% of patients treated with Alecensa; the most frequent adverse reactions (⩾ 2%) that led to dose reductions and interruptions were increased blood creatine phosphokinase (6.3% and 5.5%), increased blood bilirubin (both 3.9%), increased ALT (1.6% and 5.5%), increased AST (0.8% and 4.7%) and myalgia (1.6% and 2.3%), respectively.

Table 3 summarises the common adverse reactions observed in ALINA.

Table 3: Adverse Drug Reactions (≥ 10% for all NCI CTCAE Grades or ≥ 2% for Grades 3-4) in Patients Treated with Alecensa in ALINA

Adverse Reaction	**Alecensa N = 128**		**Chemotherapy N = 120**	
	All Grades (%)	**Grades 3-4 (%)**	**All Grades (%)**	**Grades 3-4 (%)**
Gastrointestinal Disorders				
Constipation	42	0.8*	25	0.8
Diarrhoea	13	0.8*	8	0.8
Musculoskeletal				
Myalgia[a]	34	0.8*	3.3	0
Blood and Lymphatic System Disorders				
Anaemia[b]	24	0	26	0.8
Skin and Subcutaneous Tissue Disorders				
Rash[c]	17	1.6*	10	0
General Disorders and Administration Site Conditions				
Oedema[d]	16	0	1.7	0
Renal				
Renal Impairment[e]	16	0.8*	8	0
Investigations				
Increased Weight	13	0.8*	0.8	0
Nervous System Disorders				
Dysgeusia[f]	13	0	3.3	0

Cardiac Disorders				
Bradycardia[g]	12	0	0	0
Metabolism and Nutrition Disorders				
Hyperuricaemia[h]	11	0	1.7	0

Based on NCI CTCAE v5.0
[*]All events were Grade 3
[a] Includes myalgia and arthralgia
[b] Includes anaemia, normochromic normocytic anaemia and cases indicative of haemolytic anaemia.
[c] Includes rash, rash maculo-papular, dermatitis acneiform, rash papular, erythema and rash erythematous.
[d] Includes oedema, peripheral oedema, face oedema, localized oedema, peripheral swelling, face swelling.
[e] Includes increased blood creatinine, creatinine renal clearance decreased, renal impairment, renal failure and glomerular filtration rate decreased.
[f] Includes dysgeusia and taste disorder.
[g] Includes bradycardia and sinus bradycardia.
[h] includes cases of hyperuricaemia and increased blood uric acid.

The following additional clinically significant adverse reactions (< 10%) were observed in patients treated with Alecensa in ALINA: nausea (7.8%), vomiting (7.0%), vision disorders (4.7%; includes blurred vision, visual acuity reduced and photopsia), stomatitis (4.7%; includes stomatitis and mouth ulceration), photosensitivity reaction (3.9%) and pneumonitis (2.3%).

Locally advanced or metastatic treatment of ALK-positive NSCLC

Table 4 lists the adverse drug reactions (ADRs) occurring in patients who received Alecensa in clinical trials for locally advanced or metastatic ALK-positive NSCLC.

ADRs from clinical trials are listed by MedDRA system organ class. The corresponding frequency category for each ADR is based on the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000).

Table 4: ADRs occurring in patients treated with Alecensa in Phase II clinical trials (NP28673 and NP28761) and Phase III clinical trial BO28984

Adverse Drug Reactions (MedDRA)	**Alecensa N=253 (NP28673 and NP28761)/N=152 (BO28984)[#]**		
System Organ Class	**All Grades (%)**	**Frequency category (All Grades)**	**Grade 3-4 (%)**
Gastrointestinal disorders			
Constipation	36	very common	0
Nausea	22	very common	0.7[#]
Diarrhoea	18	very common	1.2
Vomiting	13	very common	0.4
Stomatitis[1]	3.3[#]	common	0[#]

General disorders and administration site conditions			
Oedema[2]	34	very common	0.8
Musculoskeletal and connective tissue disorders			
Myalgia[3]	31	very common	1.2
Increased blood creatine phosphokinase	13	very common	3.6
Hepatobiliary disorders			
Increased bilirubin[4]	21[#]	very common	3.3[#]
Increased AST	16	very common	5.3[#]
Increased ALT	15[#]	very common	4.6[#]
Drug-induced liver injury[5]	0.8	uncommon	0.8
Skin and subcutaneous tissue disorders			
Rash[6]	20	very common	0.7[#]
Photosensitivity reaction	12	very common	0.7[#]
Blood and lymphatic system disorders			
Anaemia[7]	20[#]	very common	4.6[#]
Eye disorders			
Vision disorders[8]	12	very common	0
Cardiac disorders			
Bradycardia[9]	11[#]	very common	0
Investigations			
Weight increased[#]	9.9[#]	common	0.7[#]
Renal and urinary disorders			
Increased blood creatinine	7.9[#]	common	1.3[#*]
Acute kidney injury[#]	2.6[#]	common	2.6[#*]
Nervous System Disorders			
Dysgeusia[#10]	3.3[#]	common	0.7[#]
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease/pneumonitis	1.3[#]	common	0.4

[#] Event and/or rate reported in study BO28984 (N=152 patients treated with Alecensa); remainder of events and/or rates reported in trials NP28761, NP28673 (N=253 patients treated with Alecensa)

[*] Includes one Grade 5 event

[1] Includes cases of stomatitis and mouth ulceration

[2] Includes cases of peripheral oedema, oedema, generalised oedema, eyelid oedema, periorbital oedema

[3] Includes cases of myalgia and musculoskeletal pain

[4] Includes cases of increased blood bilirubin, hyperbilirubinaemia and increased bilirubin conjugated

[5] Includes one patient 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.
[6] Includes cases of rash, rash maculopapular, dermatitis acneiform, erythema, rash generalised, rash papular, rash pruritic and rash macular
[7] Includes cases of anaemia and haemoglobin decreased
[8] Includes cases of blurred vision, visual impairment, vitreous floaters, reduced visual acuity, asthenopia, and diplopia
[9] Includes cases of bradycardia and sinus bradycardia
[10] Includes cases of dysgeusia and hypogeusia

Post marketing experience

The adverse drug reaction of increased alkaline phosphatase and haemolytic anaemia were reported with Alecensa in the post marketing setting, as well as during clinical trials.

Description of selected adverse drug reactions

The safety profile of Alecensa was generally consistent across the clinical trials (BO40336, BO28984, NP28673 and NP28761); however, relevant differences between studies are described below.

Interstitial Lung Disease (ILD)/Pneumonitis
ILD/pneumonitis occurred in 1.3% of patients treated with Alecensa across clinical trials. In 0.4% of the patients, the event was Grade 3, and in 0.9% of patients, the event led to treatment discontinuation. There were no fatal cases of ILD/pneumonitis in any of the clinical trials.

Hepatotoxicity
Across clinical trials, 0.6% of patients had a documented drug-induced liver injury (including 2 patients with the reported term drug-induced liver injury and 1 patient with reported Grade 4 increased AST and ALT who had documented drug-induced liver injury by liver biopsy). Adverse reactions of increased AST and ALT levels (22.7% and 20.1% respectively) were reported in patients treated with Alecensa across the clinical trials. The majority of these events were of Grade 1 and 2 intensity, and events of Grade ≥ 3 were reported in 3.0% and 3.2% of the patients, respectively. The events generally occurred during the first 3 months of treatment, were usually transient and resolved upon temporary interruption of Alecensa treatment (reported for 2.3% and 3.6% of the patients, respectively) or dose reduction (1.7% and 1.5%, respectively). In 1.1% and 1.3% of the patients, AST and ALT elevations, respectively, led to discontinuation of Alecensa treatment.

Adverse reactions of bilirubin elevations were reported in 25.1% of the patients treated with Alecensa across clinical trials. The majority of the events were of Grade 1 and 2 intensity; Grade ≥ 3 events were reported in 3.4% of the patients. The events generally occurred during the first 3 months of treatment, were usually transient and the majority resolved upon dose modification. In 7.7% of patients, bilirubin elevations led to dose modifications and in 1.5% of patients, bilirubin elevations led to discontinuation of Alecensa treatment.

Concurrent elevations in ALT or AST greater than or equal to three times the ULN and total bilirubin greater than or equal to two times the ULN, with normal alkaline phosphatase, occurred in 1 patient treated in Alecensa clinical trials.

Bradycardia
Cases of bradycardia (11.1%) have been reported in patients treated with Alecensa across clinical trials; all cases were of Grade 1 or 2 intensity. There were 102 of 521 patients (19.6%) treated with Alecensa, for whom serial ECGs were available, who had post-dose heart rate values below 50 beats per minute [bpm].

Severe Myalgia and CPK Elevation
Cases of myalgia (34.9%) including myalgia events (24.0%), arthralgia (16.1%) and musculoskeletal pain (0.9%) have been reported in patients treated with Alecensa across clinical trials. The majority of the events were Grades 1 or 2; 0.9% of patients had a Grade 3 event. Dose modifications due to these events were required for 1.7% of patients.

Elevations of CPK occurred in 55.6% of 491 patients with CPK laboratory data available in clinical trials with Alecensa. The incidence of ≥ Grade 3 elevations of CPK was 5.5% across the clinical trials. Median time to ≥ Grade 3 CPK elevation was 15 days. Dose modifications for elevation of CPK occurred in 5.3% of patients.

Haemolytic Anemia
Haemolytic anemia has been observed in 3.1% of patients treated with Alecensa in the clinical trial setting. These cases were Grade 1 or 2 (non-serious) and did not lead to treatment discontinuation.

Laboratory Abnormalities

Table 5 summarises the most common treatment-emergent shifts in key laboratory abnormalities occurring in patients who received Alecensa in phase III clinical trial BO40336 (ALINA).

Table 5: Treatment-Emergent Worsening in Laboratory Values from Baseline occurring in ⩾ 20% of Patients in Treated with Alecensa in ALINA

Parameter	Alecensa N= 128		Chemotherapy N=120	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Chemistry				
Increased CPK	77	8	8	1.7
Increased AST	75	0.8*	25	0
Increased bilirubin	68	2.3*	4.2	0
Increased alkaline phosphatase	64	0	14	0
Increased ALT	57	2.3*	28	0

Increased creatinine	41	0	23	0
Increased uric acid	30	0	19	0
Haematology				
Decreased haemoglobin	69	0	67	0.8

Based on NCI CTCAE v5.0
*All events were Grade 3

Table 6 summarises the most common treatment-emergent shifts in key laboratory abnormalities occurring in patients who received Alecensa in phase II clinical trials (NP28673 and NP28761) and phase III clinical trial BO28984.

Table 6: Alecensa treatment-emergent shifts in key laboratory abnormalities in Phase II clinical trials (NP28673 and NP28761) and Phase III clinical trial BO28984

Parameter	**Alecensa N=250*/N=152#**	
	All Grades (%)	**Grade 3 -4° (%)**
Chemistry		
Increased AST	53*	6.2#
Increased blood bilirubin	53#	5.5#
Increased blood CPK[a]	46*	5.0*
Increased ALT	40#	6.1#
Increased blood creatinine**	38#	3.4#
Haematology		
Decreased haemoglobin	62#	6.8#

AST=aspartate aminotransferase; CPK=creatine phosphokinase; ALT=alanine aminotransferase
Note: Laboratory abnormalities were based on the normal ranges of the NCI CTCAE
* Rate reported in NP28761 and NP28673 studies; N=219 for CPK.
# Rate reported in study BO28984; Patients with missing baseline and/or no post-baseline lab assessments were excluded from analyses; N=147 for blood creatinine, ALT and haemoglobin; N=145 for AST; N=146 for blood bilirubin.
** Only patients with creatinine increases based on ULN definition (CTCAE grading).
° No Grade 5 laboratory abnormalities were reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions (https://pophealth.my.site.com/carmreportnz/s/).

4.9 Overdose

No experience with overdosage is available from the pivotal clinical trials and there is no specific antidote for overdosage with Alecensa. Patients who experience overdose should be

closely supervised and supportive care instituted. Alectinib is more than 99% bound to plasma proteins and haemodialysis is likely to be ineffective in the treatment of overdose. For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-neoplastic agents, protein kinase inhibitor; ATC code: L01ED03.

Mechanism of action

Alectinib is a tyrosine kinase inhibitor that targets anaplastic lymphoma kinase (ALK) and Rearranged during Transfection (RET) tyrosine kinase.

In nonclinical studies, alectinib inhibits ALK tyrosine kinase activity, leading to blockage of downstream signalling pathways including STAT3 and PI3K/AKT, and inhibits proliferation of cancer cells harbouring ALK fusion proteins.

Alectinib demonstrated *in vitro* and *in vivo* activity against mutant forms of ALK, including some that have been identified in non-small cell lung cancer (NSCLC) tumours in patients who progressed on crizotinib. The major active metabolite of alectinib (M4) showed similar *in vitro* potency and activity.

Administration of alectinib to mice implanted with ALK-rearranged tumour cell line xenografts, including some that received intracranial xenografts, resulted in anti-tumour activity and prolonged survival.

Clinical efficacy and safety

Adjuvant treatment of resected ALK-positive non-small cell lung cancer (NSCLC)

The efficacy of Alecensa for the adjuvant treatment of patients with ALK-positive NSCLC following complete tumour resection was established in a global randomised Phase III open-label clinical trial (BO40336; ALINA). Eligible patients were required to have Stage IB (tumours $\geqslant$ 4 cm) – IIIA NSCLC per the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) Staging System, 7th Edition, with ALK-positive disease identified by a locally performed FDA-approved or CE-marked ALK test, or centrally performed by the Ventana ALK (D5F3) immunohistochemistry (IHC) assay.

Patients were randomised (1:1) to receive Alecensa or platinum-based chemotherapy following tumour resection. Randomisation was stratified by race (Asian and non-Asian) and stage of disease (IB, II and IIIA). Alecensa was administered at the recommended oral dose of 600 mg twice daily for a total of 2 years, or until disease recurrence or unmanagable toxicity. Platinum-based chemotherapy was administered intravenously for 4 cycles, with each cycle lasting 21 days, according to one of the following regimens:

- Cisplatin 75 mg/m^2 on Day 1 plus vinorelbine 25 mg/m^2 on Days 1 and 8
- Cisplatin 75 mg/m^2 on Day 1 plus gemcitabine 1250 mg/m^2 on Days 1 and 8
- Cisplatin 75 mg/m^2 on Day 1 plus pemetrexed 500 mg/m^2 on Day 1

In the event of intolerance to a cisplatin-based regimen, carboplatin was administered instead of cisplatin in the above combinations at a dose of area under the free carboplatin plasma concentration versus time curve (AUC) 5 mg/mL/min or 6 mg/mL/min.

The primary efficacy endpoint was disease-free survival (DFS) as assessed by the Investigator. DFS was defined as the time from the date of randomisation to the date of occurrence of any of the following: first documented recurrence of disease, new primary NSCLC, or death due to any cause, whichever occurred first. The secondary and exploratory efficacy endpoints were overall survival (OS) and time to CNS recurrence or death (CNS-DFS).

A total of 257 patients were studied; 130 patients were randomised to the Alecensa arm, and 127 patients were randomised to the chemotherapy arm. Overall, the median age was 56 years (range: 26 to 87), 24% were ≥ 65 years old, 52% were female, 56% were Asian, 60% were never smokers, 53% had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0, 10% of patients had Stage IB, 36% had Stage II and 54% had Stage IIIA disease.

ALINA demonstrated a statistically significant and clinically meaningful improvement in DFS for patients treated with Alecensa compared to patients treated with chemotherapy in the Stage II-IIIA and the Stage IB-IIIA (ITT) patient populations. OS data were not mature at the time of DFS analysis with 2.3% of deaths reported overall. The median duration of survival follow-up was 27.8 months in the Alecensa arm and 28.4 months in the chemotherapy arm.

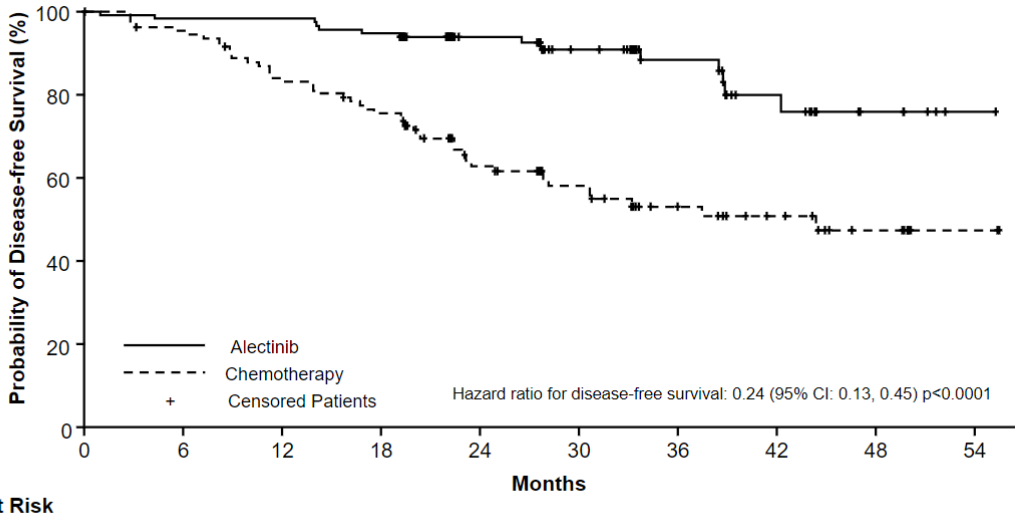
The DFS efficacy results are summarised in Table 7, and Figure 1 and Figure 2.

Table 7: Investigator Assessed DFS Results in ALINA

Efficacy Parameter	**Stage II-IIIA Population**		**ITT Population**	
	Alecensa N=116	**Chemotherapy N=115**	**Alecensa N=130**	**Chemotherapy N=127**
Number of DFS Events (%)	14 (12.1)	45 (39.1)	15 (11.5)	50 (39.4)
Median DFS, months (95% CI)	NE (NE, NE)	44.4 (27.8, NE)	NE (NE, NE)	41.3 (28.5, NE)
Stratified HR (95% CI)*	0.24 (0.13, 0.45)		0.24 (0.13, 0.43)	
p-value (log-rank)*	<0.0001		<0.0001	
2 Year Event Free Rate, % (95% CI)	93.8 (89.4, 98.3)	63.0 (53.3, 72.7)	93.6 (89.4, 97.9)	63.7 (54.6, 72.9)
3 Year Event Free Rate, % (95% CI)	88.3 (80.8, 95.8)	53.3 (42.3, 64.2)	88.7 (81.8, 95.6)	54.0 (43.7, 64.2)

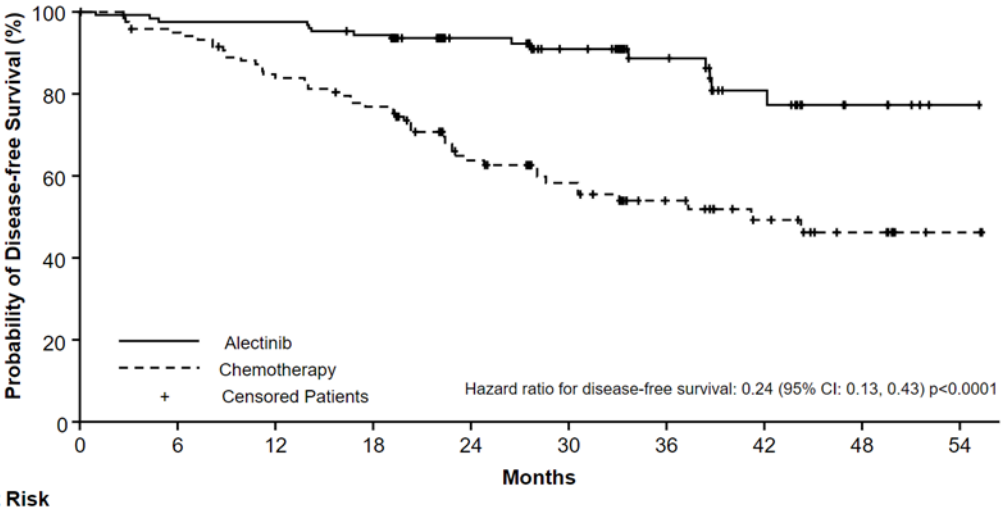
DFS = Disease-Free Survival; ITT = Intent-to-Treat; CI = Confidence Interval; NE = Not Estimable; HR = Hazard Ratio *Stratified by race in Stage II-IIIA, stratified by race and stage in Stage IB-IIIA.

Figure 1: Kaplan-Meier Curve of Disease-Free Survival in the Stage II – IIIA Population



Patients at Risk										
Alectinib	116	111	111	107	67	49	35	21	10	3
Chemotherapy	115	102	88	79	48	35	23	17	10	2

Figure 2: Kaplan-Meier Curve of Disease-Free Survival in the ITT Population



Patients at Risk										
Alectinib	130	123	123	118	74	55	39	22	10	3
Chemotherapy	127	112	98	89	55	41	27	18	11	2

An exploratory analysis of CNS-DFS for patients receiving Alecensa compared to patients receiving chemotherapy showed a HR of 0.22 (95% CI: 0.08, 0.58) in the ITT population. An exploratory analysis of the site(s) of relapse showed the proportion of patients with brain involvement at the time of disease recurrence was 4 patients (3.1%) in the Alecensa arm and 14 patients (11.0%) in the chemotherapy arm in the ITT population.

Treatment of locally advanced or metastatic ALK-positive NSCLC

Treatment-naïve patients

The safety and efficacy of Alecensa were studied in a global randomised Phase III open label clinical trial [BO28984 (ALEX)] in ALK-positive NSCLC patients not previously treated systemically for advanced or metastatic NSCLC. Central testing for ALK protein expression positivity of tissue samples from all patients by Ventana anti-ALK (D5F3) immunohistochemistry (IHC) was required before randomisation into the study.

A total of 303 patients were included in the Phase III trial, 151 patients randomised to the crizotinib arm and 152 patients randomised to the Alecensa arm receiving Alecensa orally, at the recommended dose of 600 mg twice daily.

ECOG performance status (0/1 vs. 2), race (Asian vs. non-Asian), and CNS metastases at baseline (yes vs. no) were stratification factors for randomisation. The primary endpoint of the trial was to demonstrate superiority of Alecensa versus crizotinib based on Progression Free Survival (PFS) as per investigator assessment using RECIST 1.1. Baseline demographic and disease characteristics for Alecensa were median age 58 years (54 years for crizotinib), 55% female (58% for crizotinib), 55% non-Asian (54% for crizotinib), 61% with no smoking history (65% for crizotinib), 93% ECOG performance status of 0 or 1 (93% for crizotinib), 97% Stage IV disease (96% for crizotinib), 90% adenocarcinoma histology (94% for crizotinib), 40% CNS metastases at baseline (38% for crizotinib) and 17% having received prior CNS radiation (14% for crizotinib).

The trial met its primary endpoint at the primary analysis. Efficacy data are summarised in Table 8 and the Kaplan-Meier curves for investigator and Independent Review Committee (IRC)-assessed PFS are shown in Figures 3 and 4.

Table 8. Summary of efficacy results from study BO28984 (ALEX)

	Crizotinib N=151	**Alecensa N=152**
Median duration of follow-up (months)	17.6 (range 0.3 – 27.0)	18.6 (range 0.5 – 29.0)
Primary Efficacy Parameter		
PFS (INV)		
Number of patients with event n (%)	102 (68%)	62 (41%)
Median (months)	11.1	NE
[95% CI]	[9.1; 13.1]	[17.7; NE]
HR	0.47	
[95% CI]	[0.34, 0.65]	
Stratified log-rank p-value	p <0.0001	
Secondary efficacy parameters		
PFS (IRC)*		
Number of patients with event n (%)	92 (61%)	63 (41%)

Median (months) [95% CI]	10.4 [7.7; 14.6]	25.7 [19.9; NE]
HR [95% CI] Stratified log-rank p-value	0.50 [0.36; 0.70] p < 0.0001	
Time to CNS progression (IRC)* (without prior systemic PD**) Number of patients with event n (%)	 68 (45%)	 18 (12%)
Cause-Specific HR [95% CI] Stratified log-rank p-value	0.16 [0.10; 0.28] p < 0.0001	
12-month cumulative incidence of CNS progression (IRC) % (95% CI)	41.4% [33.2; 49.4]	9.4% [5.4; 14.7]
ORR (INV)*, *** Responders n (%) [95% CI]	 114 (75.5%) [67.8; 82.1]	 126 (82.9%) [76.0; 88.5]
Overall survival* Number of patients with event n (%)* Median (months) [95% CI]	 40 (27%) NE [NE; NE]	 35 (23%) NE [NE; NE]
HR [95% CI]	0.76 [0.48; 1.20]	
Duration of response (INV) Median (months) 95 % CI	N=114 11.1 [7.9; 13.0]	N=126 NE [NE; NE]
CNS-ORR in patients with measurable CNS metastases at baseline CNS responders n (%) [95% CI] CNS-CR n (%) CNS-DOR , median (months) 95% CI	N=22 11 (50.0%) [28.2; 71.8] 1 (5%) 5.5 [2.1, 17.3]	N=21 17 (81.0%) [58.1; 94.6] 8 (38%) 17.3 [14.8, NE]
CNS-ORR in patients with measurable and non-measurable CNS metastases at baseline (IRC) CNS responders n (%) [95% CI] CNS-CR n (%) 3.7	N=58 15 (25.9%) [15.3%; 39.0%] 5 (9%) 	N=64 38 (59.4%) [46.4%; 71.5%] 29 (45%) NE

CNS-DOR , median (months) 95% CI	[3.2, 6.8]	[17.3, NE]

* Key secondary endpoints part of the hierarchical testing

** Competing risk analysis of CNS progression, systemic progression and death as competing events

*** 2 patients in the crizotinib arm and 6 patients in the alectinib arm had CR

CI = confidence interval; CNS = central nervous system; CR = complete response; DOR = duration of response; HR = hazard ratio; IRC = Independent Review Committee; INV = investigator; NE = not estimable; ORR = objective response rate; PFS = progression-free survival

The magnitude of PFS benefit was consistent for patients with CNS metastases at baseline (HR=0.40, 95% CI: 0.25-0.64, median PFS for Alecensa = NE, 95% CI: 9.2-NE, median PFS for crizotinib = 7.4 months, 95% CI: 6.6-9.6) and without CNS metastases at baseline (HR = 0.51, 95% CI: 0.33-0.80, median PFS for Alecensa = NE, 95% CI: NE, NE, median PFS for crizotinib = 14.8 months, 95% CI:10.8-20.3), indicating benefit of Alecensa over crizotinib in both subgroups.

Figure 3: Kaplan Meier Plot of INV-Assessed PFS in study BO28984 (ALEX)

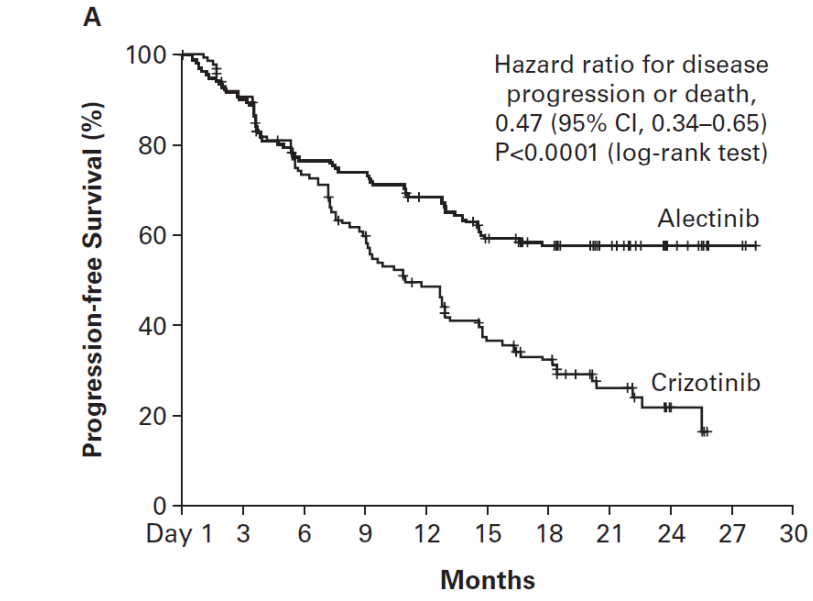
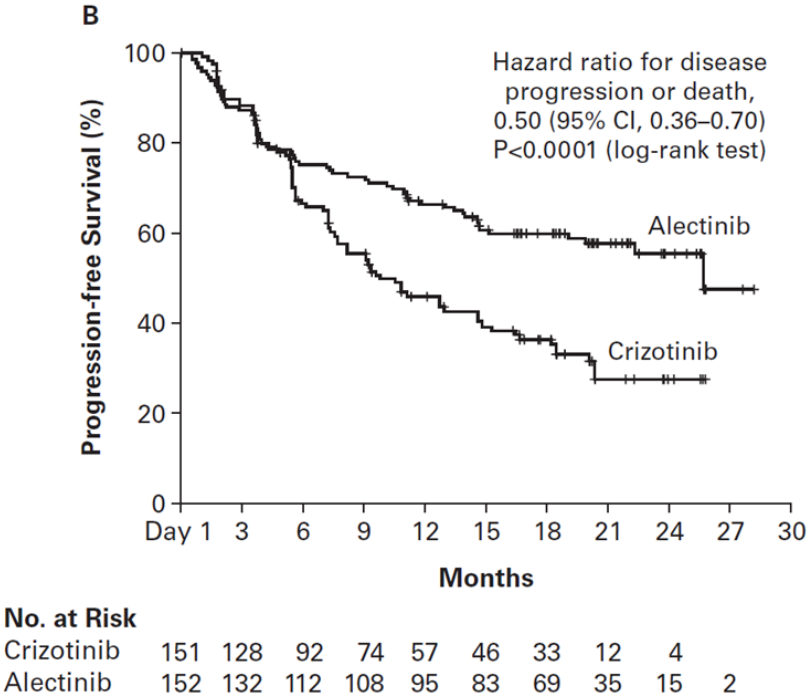


Figure 4: Kaplan Meier Plot of IRC Assessed PFS in study BO28984 (ALEX)



Crizotinib pre-treated patients

The safety and efficacy of Alecensa in ALK-positive NSCLC patients pre-treated with crizotinib were studied in two Phase I/II clinical trials (NP28673 and NP28761).

Study NP28673

Study NP28673 was a Phase I/II single arm, international, multicentre study conducted in patients with ALK-positive advanced NSCLC who have previously progressed on crizotinib. In addition to crizotinib, patients may have received previous treatment with chemotherapy. A total of 138 patients were included in the phase II part of the study and received Alecensa orally at the recommended dose of 600 mg twice daily.

The primary endpoint was to evaluate the efficacy of Alecensa by objective response rate (ORR) as per central independent review committee (IRC) assessment using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 in the overall population (with and without prior exposure of cytotoxic chemotherapy treatments). The co-primary endpoint was to evaluate the ORR as per central IRC assessment using RECIST 1.1 in patients with prior exposure of cytotoxic chemotherapy treatments.

Patient demographics were consistent with that of a NSCLC ALK positive population. The demographic characteristics of the overall study population were 67% Caucasian, 26% Asian, 56% females and the median age was 52 years. The majority of patients had no history of smoking (70%). The Eastern Cooperative Oncology Group (ECOG) performance status at baseline was 0 or 1 in 91% of patients and 2 in 9% of patients. At the time of entry in the study, 99% of patients had stage IV disease, 61% had brain metastases and 96% of tumours

were classified as adenocarcinoma. Among patients included in the study, 20% had previously progressed on crizotinib treatment only, and 80% had previously progressed on crizotinib and chemotherapy treatment.

Study NP28761

Study NP28761 was a Phase I/II single arm, multicentre study conducted in patients with ALK-positive advanced NSCLC who have previously progressed on crizotinib treatment. In addition to crizotinib, patients may have received previous treatment with chemotherapy. A total of 87 patients were included in the phase II part of the study and received Alecensa orally at the recommended dose of 600 mg twice daily.

The primary endpoint was to evaluate the efficacy of Alecensa by ORR as per central IRC assessment using RECIST 1.1.

Patient demographics were consistent with that of a NSCLC ALK positive population. The demographic characteristics of the overall study population were 84% Caucasian, 8% Asian, 55% females and a median age of 54 years. The majority of patients had no history of smoking (62%). The ECOG performance status at baseline was 0 or 1 in 90% of patients and 2 in 10% of patients. At the time of entry in the study, 99% of patients had stage IV disease, 60% had brain metastases and 94% of tumours were classified as adenocarcinoma. Among patients included in the study, 26% had previously progressed on crizotinib treatment only, and 74% had previously progressed on crizotinib and chemotherapy treatment.

Table 9: Efficacy results from studies NP28673 and NP28761

	NP28673 Alecensa 600 mg twice daily	**NP28761 Alecensa 600 mg twice daily**
Median duration of follow-up (months)	21 (range 1 – 30)	17 (range 1 – 29)
Primary efficacy parameters		
ORR (IRC) in RE population Responders N (%) [95% CI]	N=122[a] 62 (50.8%) [41.6%, 60.0%]	N=67[b] 35 (52.2%) [39.7%, 64.6%]
ORR (IRC) in patients pre-treated with chemotherapy Responders N (%) [95% CI]	N = 96 43 (44.8%) [34.6%, 55.3%]	
Secondary efficacy parameters		
DOR (IRC) Number of patients with events N (%) Median (months) [95% CI]	N=62 36 (58.1%) 15.2 [11.2, 24.9]	N=35 20 (57.1%) 14.9 [6.9, NE]
PFS (IRC) Number of patients with events N (%) Median duration (months) [95% CI]	N=138 98 (71.0%) 8.9 [5.6, 12.8]	N=87 58 (66.7%) 8.2 [6.3, 12.6]

CI=confidence interval; DOR=duration of response; IRC=independent review committee; NE=not estimable; ORR=objective response rate; PFS=progression free survival; RE=response evaluable

[a] 16 patients did not have measurable disease at baseline according to the IRC and were not included in the IRC response evaluable population

[b] 20 patients did not have measurable disease at baseline according to the IRC and were not included in the IRC response evaluable population

A summary of the pooled analysis of the Central Nervous System (CNS) endpoints based on RECIST (IRC) performed on patients with measurable CNS lesions at baseline (N=50) included in phase II studies NP28761 and NP28673 is presented in Table 10.

Table 10: Summary of the pooled analysis of CNS endpoints from studies NP28673 and NP28761

CNS Parameters (NP28673 and NP28761)	**Alecensa 600 mg twice daily**
Patients with measurable CNS lesions at baseline	N=50
CNS ORR (IRC) Responders (%) [95% CI] Complete response Partial response	 32 (64.0%) [49.2%, 77.1%] 11 (22.0%) 21 (42.0%)
CNS DCR (IRC) CR+PR+SD[a] [95% CI]	 45 (90.0%) [78.2%, 96.7%]
CNS DOR (IRC) Number of patients with events (%) Median (months) [95%CI]	N=32 18 (56.3%) 11.1 [7.6, NE]

CI=confidence interval; CR=complete response; DCR= disease control rate; DOR=duration of response; IRC=independent review committee; NE= not estimable ; ORR=objective response rate; PR=partial response; SD=stable disease

[a] DCR calculated including all patients who achieved a Best Overall Response (BOR) of SD (minimum duration of 5 weeks as per IRC Charter).

5.2 Pharmacokinetic properties

The pharmacokinetic (PK) parameters for alectinib and its major active metabolite (M4) have been characterised in healthy subjects and in patients with ALK-positive NSCLC. The results for patients with ALK-positive NSCLC are summarised in Table 11.

Table 11: Steady-state PK seen with recommended 600 mg twice daily dosing of alectinib [cited as geometric mean (coefficient of variation %)]

PK parameter	**Alectinib**	**M4**
Maximal concentration (C_{max})	665 ng/mL (44.3%)	246 ng/mL (45.4%)
Trough concentration (C_{min})	572 ng/mL (47.8%)	222 ng/mL (46.6%)
Area under the curve from 0-12 hours (AUC_{0-12})	7430 ng*h/mL (45.7%)	2810 ng*h/mL (45.9%)

Absorption

The absolute bioavailability of alectinib was 36.9% (90% CI: 33.9%, 40.3%) under fed conditions in healthy subjects.

Alectinib reached maximal serum concentrations 4 to 6 hours post-dose when administered orally at 600 mg twice daily under fed conditions to patients with ALK-positive NSCLC. For both alectinib and M4, steady-state concentrations were reached by Day 7.

Population PK analysis estimated geometric mean accumulation ratio to be 6-fold for both alectinib and M4, and supports that alectinib exposure is dose proportional across the dose range 300 mg to 900 mg under fed conditions.

A high-fat, high-calorie meal increased the combined exposure of alectinib and M4 by 3-fold ($AUC_{0\text{-}inf}$ 3.1 [90% CI: 2.7, 3.6]) relative to fasted conditions following oral administration of a single 600 mg dose of alectinib.

Distribution

Alectinib and M4 are highly bound to human plasma proteins (>99%), independent of drug concentration. The mean *in vitro* human blood-to-plasma concentration ratios of alectinib and M4 are 2.64 and 2.50, respectively, at clinically relevant concentrations. The geometric mean volume of distribution at steady state (V_{ss}) of alectinib following IV administration was 475 L, indicating extensive distribution into tissues.

Alectinib is not an *in vitro* substrate of efflux transporters P-gp, BCRP, OATP 1B1 or OATP 1B3. The same is true for M4, except that M4 is a substrate of P-gp. Alectinib concentrations in the cerebrospinal fluid of patients with ALK-positive NSCLC were similar to the estimated free alectinib concentrations in their plasma.

Biotransformation

In vitro studies showed that alectinib is mainly metabolised by CYP3A4 (40-50% of alectinib metabolism in human hepatocytes) to its major active metabolite M4. The geometric mean metabolite/parent exposure ratio at steady-state is 0.40. M4 is subsequently metabolised by CYP3A4. Results from a human mass balance study utilising ^{14}C-labelled alectinib demonstrated that alectinib and M4 are the main circulating moieties in plasma, constituting 76% of the total radioactivity.

Elimination

Following administration of a single oral dose of ^{14}C-labelled alectinib to healthy subjects, the majority of radioactivity was excreted in faeces (mean recovery 97.8%, range 95.6%-100%). Most of the dose (84%) was excreted as unchanged alectinib with 6% excreted as M4. There was minimal excretion in urine (mean recovery 0.46%, range 0.30%-0.60%).

Based on a population PK analysis, the apparent clearance (CL/F) was 81.9 L/hour for alectinib and 217 L/hour for M4. The geometric mean elimination half-life was 32.5 hours for alectinib and 30.7 hours for M4 in patients with ALK-positive NSCLC.

Pharmacokinetics in Special Populations

Population PK analysis of data from two Phase I/II clinical trials (NP28673 and NP28761) was undertaken to characterise the PK of alectinib and M4 in special populations.

Effects of age, body weight, race and gender

Age, body weight, race and gender had no clinically meaningful effect on the systemic exposure of alectinib and M4 in the range of exposure achieved with the recommended 600 mg twice daily dose. The pharmacokinetics of alectinib has not been studied in children.

Hepatic impairment

Elimination of alectinib is predominantly through hepatic metabolism. Mild hepatic impairment had no clinically meaningful effect on the systemic exposure of alectinib and M4. Mild hepatic impairment is defined as baseline total bilirubin (Br) ≤ the upper limit of normal (ULN) and baseline aspartate aminotransferase (AST) > ULN or baseline total Br > 1.0 to 1.5 times ULN and any baseline AST.

Following administration of a single oral dose of 300 mg alectinib in subjects with moderate (Child-Pugh B) hepatic impairment, the combined exposure of alectinib and M4 was modestly increased compared with matched healthy subjects (geometric mean ratio [90% confidence interval] for moderate/healthy: C_{max}: 1.16 [0.786 – 1.72], AUC_{inf}: 1.36 [0.947 – 1.96)]. Administration of a single oral dose of 300 mg alectinib in subjects with severe (Child-Pugh C) hepatic impairment resulted in a greater increase in the combined exposure of alectinib and M4 compared with matched healthy subjects (geometric mean ratio [90% confidence interval] for severe/healthy: C_{max}: 0.981 [0.517 – 1.86], AUC_{inf}: 1.76 [0.984 – 3.15]).

No dose adjustments are required for Alecensa in patients with underlying mild or moderate hepatic impairment. Patients with underlying severe hepatic impairment should receive a dose of 450 mg given orally twice daily (total daily dose of 900 mg).

Renal impairment

Mild to moderate renal impairment (creatinine clearance 30 to 89 mL/min) had no clinically meaningful effect on the systemic exposure of alectinib and the active metabolite M4. No dose adjustment is required in mild to moderate renal impairment. Negligible amounts of alectinib and M4 are excreted unchanged in urine (<0.2% of the dose). The pharmacokinetics of alectinib has not been studied in patients with severe renal impairment, however due to the negligible renal clearance of alectinib, no dose adjustment is required in severe renal impairment.

5.3 Preclinical safety data

Genotoxicity

Alectinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay but induced a slight increase in numerical aberrations in the *in vitro* cytogenetic assay using Chinese Hamster Lung cells with metabolic activation, and micronuclei in a rat bone marrow micronucleus test. The mechanism of micronucleus induction was abnormal chromosome segregation (aneugenicity), and not a clastogenic effect on chromosomes.

Carcinogenicity

Carcinogenicity studies have not been performed to establish the carcinogenic potential of Alecensa.

Effects on fertility

No fertility-specific studies of alectinib in animals have been performed. No adverse effects on male and female reproductive organs were observed in general toxicology studies conducted in rats and monkeys at exposures equal to or greater than 2.6 and 0.5 fold, respectively, of the human exposure measured by AUC at the recommended dose of 600 mg twice daily.

Reproductive toxicity

In animal studies, a maternal dose of alectinib (27 mg/kg/day) equivalent to 2.7-times the recommended human dose of 600 mg twice-daily (based on AUC) caused embryo-fetal loss (miscarriage), visceral malformation (retro-oesophageal subclavian) and skeletal variations (an increase in full supernumerary ribs and a corresponding decrease in short supernumerary ribs) in pregnant rabbits. The same dose given to pregnant rats (4 times the clinical AUC) resulted in total litter loss. Alectinib at 9 mg/kg/day (2.5 times the clinical AUC) caused small fetuses and fetal abnormalities (dilated ureter, thymic cord, small ventricle and thin ventricle wall of the heart, and decreased number of sacral and caudal vertebrae).

Other

Alectinib absorbs UV light between 200 and 400 nm and demonstrated phototoxic potential in an *in vitro* photosafety test in cultured murine fibroblasts after UVA irradiation.

Juvenile animal studies have not been conducted using alectinib. In general toxicology studies, treatment of rats with alectinib doses of ≥ 27 mg/kg/day ($AUC_{0\text{-}24h}$ 38200 ng.h/mL) resulted in changes in the growing teeth and bones. Findings in teeth included discolouration and changes in tooth size along with histopathological disarrangement of the ameloblast and odontoblast layers and degeneration/necrosis of ameloblasts. There were also decreases in the trabecular bone and increased osteoclast activity in the femur and sternum. Increased plasma

alkaline phosphatase (ALP) of the bone isoform was observed at alectinib doses ≥ 6 mg/kg/day ($AUC_{0\text{-}24h}$ 13900 ng.h/mL).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Lactose monohydrate
Hyprolose
Sodium lauryl sulfate
Carmellose calcium
Magnesium stearate

Capsule shell

Carrageenan
Potassium chloride
Titanium dioxide (E171)
Carnauba wax
Maize starch
Hypromellose

Printing ink

Iron oxide red (E172)
Iron oxide yellow (E172)
Indigo carmine aluminium lake (E132)
Carnauba wax
Shellac
Glyceryl monooleate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store below 30°C. Store in the original package to protect from light and moisture.

6.5 Nature and contents of container

Aluminum foil blister sealed with an aluminum lidding foil containing 8 capsules per blister.

Pack size: 224 (4 packs of 56) capsules.

6.6 Special precautions for disposal

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

7 MEDICINE SCHEDULE

Prescription

8 SPONSOR

Roche Products (New Zealand) Limited
PO Box 109113 Newmarket
Auckland 1149
NEW ZEALAND

Medical enquiries: 0800 656 464

9 DATE OF FIRST APPROVAL

21 December 2017

10 DATE OF REVISION OF THE TEXT

11 December 2024

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.6	Increase in contraception requirements for female patients of childbearing potential from 1 week post last dose of Alecensa to 5 weeks post last dose.