Alecensa®

Alectinib

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Antineoplastic agent, protein kinase inhibitor
ATC code: L01ED03

1.2 Type of Dosage Form

Alectinib hard capsules, 150 mg are white, Size 1 capsules with "ALE" printed in black ink on the cap and "150 mg" printed in black ink on the body.

1.3 Route of Administration

Oral

1.4 Sterile / Radioactive Statement

Not applicable

1.5 Qualitative and Quantitative Composition

Active ingredient: Alectinib
Each hard capsule contains: Alectinib 150 mg (equivalent to 161.3 mg alectinib hydrochloride).
Excipients:
Capsule content: lactose monohydrate, hydroxypropylcellulose, sodium lauryl sulfate, magnesium stearate, carboxymethylcellulose calcium
Capsule shell: hypromellose, carrageenan, potassium chloride, titanium dioxide (E171), corn starch, carnauba wax
Printing ink: red iron oxide (E172), yellow iron oxide (E172), FD&C Blue No. 2, aluminum lake (E132), carnauba wax, white shellac, glyceryl monooleate, 1-butanol, dehydrated ethyl alcohol

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication

Adjuvant Treatment of Resected Non-Small Cell Lung Cancer
Alecensa as monotherapy is indicated as adjuvant treatment following complete tumor resection for adult patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) at high risk of recurrence (see section 3.1.2).

Treatment of Locally Advanced or Metastatic NSCLC
Alecensa is indicated for the first-line treatment of patients with ALK-positive locally advanced or metastatic NSCLC.

Alecensa is indicated for the treatment of patients with ALK-positive, locally advanced or metastatic NSCLC who have progressed on or are intolerant to crizotinib.

2.2 Dosage and Administration

General
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.
Alecensa hard capsules should be taken with food. Capsules should be swallowed whole and must not be opened or dissolved.
The recommended dose of Alecensa is 600 mg (four 150 mg capsules) given orally, twice daily (total daily dose of 1200 mg) *(see section 3.2 Pharmacokinetic Properties)*.
Patients with underlying severe hepatic impairment should receive a dose of 450 mg given orally twice daily (total daily dose of 900 mg) (*see sections 2.2.1 Special Dosing Instructions and 3.2.5 Pharmacokinetics in Special Populations*)

Duration of Treatment
Adjuvant Treatment of Resected NSCLC
It is recommended that patients are treated with Alecensa until disease recurrence or 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
If a dose of Alecensa is missed or vomiting occurs after taking a dose of Alecensa, patients should take the next dose at the scheduled 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. Alecensa treatment should be permanently discontinued if patients are unable to tolerate the 300 mg twice-daily dose.
Table 1 below gives general dose modification advice for Alecensa.

Table 1: Dose Reduction Schedule

Dose reduction schedule	Dose level
Dose	600 mg twice daily
First dose reduction	450 mg twice daily
Second dose reduction	300 mg twice daily

Table 2: Dose Modification Advice for Specified Adverse Drug Reactions *(see sections 2.4.1 Warnings and Precautions and 2.6 Undesirable Effects)*

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
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 hemolysis	Permanently discontinue Alecensa
Bradycardia[a] Grade 2 or Grade 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 discontinue, 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.
Total bilirubin elevation of greater than 3 times ULN	Temporarily withhold until recovery to baseline or to less than or equal to 1.5 times ULN, then resume at reduced dose as per Table 1.
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 of > 5 times ULN	Temporarily withhold until recovery to baseline or to ≤ 2.5 times ULN, then resume at reduced dose as per Table 1
Hemolytic anemia with hemoglobin of < 10 g/dL (Grade ≥ 2)	Temporarily withhold until resolution, resume at reduced dose (see Table 1) or permanently discontinue.
Severe hypertriglyceridemia (blood triglycerides from 501 to 1,000 mg/dL or from 5.71 to 11.4 mmol/L) OR Life-threatening hypertriglyceridemia (blood triglycerides over 1,000 mg/dL or over 11.4 mmol/L)	Temporarily withhold until recovery to at least moderate hypertriglyceridemia (i.e., until blood triglycerides are ≤ 500 mg/dL or ≤ 5.7 mmol/L). Risk factors for pancreatitis are to be evaluated, and treatable risk factors are to be addressed before resuming treatment with Alecensa. If an acute episode of pancreatitis occurs, temporarily withhold until full recovery before resuming treatment with Alecensa. Alecensa may be resumed at the same dose, with blood triglyceride levels monitored regularly in such patients.

ALT = alanine transaminase; AST = aspartate transaminase; ULN = upper limit of normal
[a]Heart rate less than 60 beats per minute (bpm)

2.2.1 Special Dosage Instructions

Pediatric use
The safety and efficacy of Alecensa in children and adolescents (<18 years) have not been studied.

Geriatric use
No dose adjustment of Alecensa is required in patients ≥65 years of age.

Renal Impairment
No dose adjustment is required in patients with mild or moderate renal impairment. Alecensa has not been studied in patients with severe renal impairment, however, since alectinib elimination via the kidney is negligible, no dose adjustment is required in patients with severe renal impairment *(see sections 2.5 Use in Special Populations and 3.2.5 Pharmacokinetics in Special Populations)*.

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 3.2.5 Pharmacokinetics in Special Populations)*.

2.3 Contraindications

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

2.4 Warnings and Precautions

2.4.1 General

Interstitial Lung Disease (ILD)/Pneumonitis
Cases of ILD/pneumonitis have been reported in clinical trials with Alecensa (*see section 2.6.1 Undesirable Effects, Clinical Trials*). Patients should be monitored for pulmonary symptoms indicative of pneumonitis. Alecensa should be immediately interrupted in patients diagnosed with ILD/pneumonitis and should be permanently discontinued if no other potential causes of ILD/pneumonitis have been identified (*see section 2.2 Dosage and Administration*).

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 (s*ee section 2.6.1 Undesirable Effects, Clinical Trials*). 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 AST/ALT 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.
Liver function, including ALT, AST, and total bilirubin should be monitored at baseline and then every 2 weeks during the first 3 months of treatment, and then periodically, since events may occur later than 3 months, 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 2.2 Dosage and Administration*).

Severe Myalgia and Creatine Phosphokinase (CPK) elevation
Myalgia or 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 2.6.1. Undesirable Effects*)
Advise patients to report any unexplained muscle pain, tenderness, or weakness. Assess CPK levels every two weeks 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 2.2 Dosage and Administration*).

Bradycardia
Symptomatic bradycardia can occur with Alecensa (*see section 2.6 Undesirable Effects*). Heart rate and blood pressure should be monitored as clinically indicated. Dose modification is not required in case of asymptomatic bradycardia (*see section 2.2 Dosage and Administration*).
If patients experience symptomatic bradycardia or life-threatening events, concomitant medications known to cause bradycardia, as well as antihypertensive medications should be evaluated and Alecensa treatment should be adjusted as described in Table 2 (*see sections 2.2 Dosage and Administration and 2.4.4 Interactions with other Medicinal Products and other Forms of Interaction, P-gp and BCRP substrates*).

Hemolytic Anemia
Hemolytic anemia has been reported with Alecensa (*see sections 2.6.1 Clinical Trials and 2.6.2 Postmarketing Experience*). If hemoglobin concentration is below 10 g/dL and hemolytic anemia is suspected, withhold Alecensa and initiate appropriate laboratory testing. If hemolytic anemia is confirmed, resume at a reduced dose upon resolution or permanently discontinue Alecensa (*see section 2.2 Dosage and Administration*)

Severe Hypertriglyceridemia
Hypertriglyceridemia, including severe cases associated with life-threatening acute pancreatitis, has been reported in patients treated with Alecensa (see sections 2.6.1 Clinical Trials and 2.6.2 Postmarketing Experience). Blood triglycerides are to be monitored before initiation and periodically during treatment. Patients are to be monitored for symptoms indicative of acute pancreatitis, especially patients at increased risk for pancreatitis.

If an acute episode of pancreatitis occurs, temporarily withhold until full recovery before resuming treatment with Alecensa. If patients experience severe or life-threatening hypertriglyceridemia, withhold Alecensa and evaluate risk factors for pancreatitis before resuming Alecensa, as described in Table 2 (see section 2.2 Dosage and Administration).

Photosensitivity
Photosensitivity to sunlight has been reported with Alecensa administration *(see section 2.6.1 Undesirable Effects, Clinical Trials)*. Patients should be advised to avoid prolonged sun exposure while taking Alecensa and for at least 7 days after discontinuation of treatment. Patients should also be advised to use a broad‑spectrum Ultraviolet A (UVA) / Ultraviolet B (UVB) sun screen and lip balm (SPF ≥50) to help protect against potential sunburn.

Embryo-fetal Toxicity
Alecensa may cause fetal harm when administered to a pregnant woman. When administrated to pregnant rats and rabbits, alectinib caused embryofetal toxicity.
Female patients of child-bearing potential must use highly effective contraceptive methods during treatment and for at least 5 weeks following the last dose of Alecensa. Women of child-bearing potential who are partners of male patients receiving Alecensa, must use highly effective contraceptive methods during treatment and for at least 3 months following the last dose of Alecensa *(see section 2.5 Use in Special Populations)*.

2.4.2 Drug Abuse and Dependence

Not applicable

2.4.3 Ability to Drive and Use Machines

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

2.5 Use in Special Populations

2.5.1 Females and Males of Reproductive Potential

Contraception
Female patients of child-bearing potential must use highly effective contraceptive methods during treatment and for at least 5 weeks following the last dose of Alecensa. Women of child-bearing potential who are partners of male patients receiving Alecensa, must use highly effective contraceptive methods during treatment and for at least 3 months following the last dose of Alecensa.

2.5.2 Pregnancy

Women of childbearing potential must be advised to avoid pregnancy while on Alecensa. No clinical studies of Alecensa in pregnant women have been performed. Based on its mechanism of action, Alecensa may cause fetal harm when administered to a pregnant woman.
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 while 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.

Animal data
In animal studies, alectinib caused embryo-fetal toxicity *(see section 3.3 Nonclinical Safety)*.

Labor and Delivery
The safe use of Alecensa during labor and delivery has not been established.

2.5.3 Lactation

It is not known whether Alecensa is excreted in human breast milk. No studies have been conducted to assess the impact of Alecensa on milk production or its presence in breast milk. As many drugs are excreted in human milk and because of the potential harm to the infant, mothers should be advised against breastfeeding while receiving Alecensa.

2.5.4 Pediatric Use
Safety and efficacy in pediatric patients below the age of 18 have not been established.

2.5.5 Geriatric Use
see section 2.2.1 Special Dosage Instructions and section 3.2.5 Pharmacokinetics in Special Populations.

2.5.6 Renal Impairment
see sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations

2.5.7 Hepatic Impairment
see sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations

2.6 Undesirable Effects
2.6.1 Clinical Trials
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 (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 adverse drug reactions (≥ 20%) adverse drug reactions (ADRs) were constipation (39.6%), myalgia (35.3% including myalgia, arthralgia and musculoskeletal pain), edema (28.5%, including peripheral, generalized, eyelid, periorbital, face, localized edema and peripheral, face, lip, joint and eyelid swelling), increased bilirubin (25.9%, including increased blood bilirubin, hyperbilirubinemia, increased bilirubin conjugated and increased blood bilirubin unconjugated), increased AST (23.6%), anemia (22.9%, including anemia, normochromic normocytic anemia, hemoglobin decreased, and cases indicative of hemolytic anemia), rash (21.2%, including rash, rash maculopapular, dermatitis, dermatitis acneiform, erythema, rash papular, rash pruritic, rash macular, exfoliative rash and rash erythematous) and increased ALT (20.5%).
Table 3 lists the ADRs by MedDRA system organ class occurring in patients who received Alecensa in the following clinical trials:NP28761, NP28673, BO28984 and BO40336 The corresponding frequency category for each adverse drug reaction 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 3: Adverse Drug Reactions Occurring in Patients Treated with Alecensa in Clinical Trials (NP28761, NP28673, BO28984 and BO40336)

Adverse Reactions (MedDRA)	**Alecensa N=533**		
System Organ Class	**All Grades (%)**	**Grades 3 – 4 (%)**	**Frequency category (all grades)**
Gastrointestinal Disorders			
Constipation	39.6	0.4	Very Common
Diarrhea	18.8	1.1	Very Common
Nausea	17.6	0.4	Very Common
Vomiting	12.4	0.2	Very Common
Stomatitis[1]	3.8	0.2	Common
General Disorders and Administration Site Conditions			
Edema[2]	28.5	0.8	Very Common
Musculoskeletal and Connective Tissue Disorders			
Myalgia[3]	35.3	0.9	Very Common
Increased Blood Creatine Phosphokinase	19.7	4.3	Very Common
Skin and Subcutaneous Tissue Disorders			
Rash[4]	21.2	1.1	Very Common
Photosensitivity Reaction	8.3	0.2	Common
Nervous System Disorders			
Dysgeusia[5]	7.3	0.2	Common
Hepatobiliary Disorders			
Increased Bilirubin[6]	25.9	3.9	Very Common
Increased AST	23.6	3.0	Very Common
Increased ALT	20.5	3.2	Very Common
Increased Alkaline Phosphatase	11.3	0.4	Very Common
Drug-Induced Liver Injury[7]	0.6	0.6	Uncommon
Blood and Lymphatic System Disorders			
Anemia[8]	22.9	3.6	Very Common
Eye Disorders			
Vision Disorders[9]	9.4	0	Common
Cardiac Disorders			
Bradycardia[10]	11.3	0	Very Common
Investigations			
Weight increased	12.9	0.8	Very Common
Renal and Urinary Disorders			
Increased Blood Creatinine	10.5	0.8*	Very common
Acute Kidney Injury	1.1	0.9*	Common
Metabolism and Nutrition Disorders			
Hypertriglyceridemia[11]	4.3	1.5	Common
Hyperuricemia[12]	3.4	0	Common
Respiratory, Thoracic and Mediastinal Disorders			
Interstitial Lung Disease/ Pneumonitis	1.7	0.4	Common

* Includes one Grade 5 event (observed in the metastatic setting).

[1] Includes cases of stomatitis and mouth ulceration
[2] Includes cases of peripheral edema, edema, generalized edema, eyelid edema, periorbital edema, face edema, localized edema, peripheral swelling, face swelling, lip swelling, swelling, joint swelling, eyelid swelling.
[3] Includes cases of myalgia, musculoskeletal pain and arthralgia.
[4] Includes cases of rash, rash maculo-papular, dermatitis, dermatitis acneiform, erythema, rash papular, rash pruritic, rash macular, exfoliative rash, rash erythematous.
[5] Includes cases of dysgeusia, hypogeusia and taste disorder.
[6] Includes cases of increased blood bilirubin, hyperbilirubinemia, increased bilirubin conjugated and increased blood bilirubin unconjugated.
[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 anemia, hemoglobin decreased, normochromic normocytic anemia and cases indicative of hemolytic anemia. [9] Includes cases of blurred vision, visual impairment, vitreous floaters, reduced visual acuity, asthenopia, diplopia, photohphobia and photopsia.
[10] Includes cases of bradycardia and sinus bradycardia.
[11] includes cases of hypertriglyceridemia and increased blood triglycerides.
[12] includes cases of hyperuricemia and increased blood uric acid.

Further Information on Selected Adverse Drug Reactions:
The safety profile of Alecensa was generally consistent across the clinical trials (BO40336, BO28984, NP28761, NP28673).Relevant differences between studies are described below.

Interstitial Lung Disease (ILD)/Pneumonitis
ILD/pneumonitis occurred in 1.7% patients treated with Alecensa across clinical trials. In 0.4% of the patients, the events were Grade 3. In 1.1% of patients, the event led to treatment discontinuation, and in 0.4% of patients, the event led to dose modifications. 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 (23.6% and 20.5%, 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 for increased AST and ALT levels, respectively. The events generally occurred during the first 3 months of treatment, were usually transient and resolved upon temporary interruption of Alecensa treatment (reported for 2.3% and 3.6% of the patients, respectively) or dose reduction (1.7% and 1.5%, respectively). In 1.3% and 1.5% of the patients, AST and ALT elevations, respectively, led to discontinuation of Alecensa treatment.
Adverse reactions of bilirubin elevations were reported in 25.9% 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 3.9% 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 8.3% of patients, bilirubin elevations led to dose modifications and in 2.1% 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 (11.3%) 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 (35.3%) including myalgia events (24.2%), arthralgia (16.3%) and musculoskeletal pain (0.8%) have been reported in patients treated with Alecensa across clinical trials. The majority of the events were Grades 1 or 2 and 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 56.2% 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 5.4% of patients.

Hemolytic Anemia
Hemolytic 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.

Hypertriglyceridemia
Hypertriglyceridemia has been observed in patients treated with Alecensa across clinical trials and through post marketing experience. In clinical trials, the majority of the events were Grade 1 or 2; Grade ≥ 3 events were reported in 1.5 % of patients. The median time to onset to Grade ≥ 3 hypertriglyceridemia events was 263 days (range: 106 to 1001 days). Dose modifications (including interruptions and/or dose reductions) due to hypertriglyceridemia occurred in 0.9 % of patients, and in 0.2 % of patients, hypertriglyceridemia led to discontinuation of Alecensa treatment.

Laboratory Abnormalities
The following table displays treatment-emergent shifts in laboratory abnormalities occurring in patients treated with Alecensa in across clinical trials (NP28761, NP28673, BO28984, BO40336).

Table 4: Alecensa Treatment-Emergent Shifts in Key Laboratory Abnormalities

Parameter	**Alectinib N=533***	
	All Grades (%)	**Grades 3 - 4(%)°**
Chemistry		
Increased AST	63.6	3.4
Increased Blood Triglycerides[#]	57.1	7.1
Increased Blood Creatine Phosphokinase	56.2	5.5
Increased Blood Alkaline Phosphatase	55.4	0.4
Increased Blood Bilirubin	55.0	4.2
Increased Blood Creatinine	47.6	1.9
Increased ALT	46.3	4.2
Increased Blood Uric Acid[&]	30.5	0
Hematology		
Decreased Hemoglobin	65.0	4.6

AST = aspartate aminotransferase, ALT = alanine aminotransferase
Note: Laboratory abnormalities were based on NCI CTCAE version 5.0.

° No Grade 5 laboratory abnormalities were reported.
* Patients without post-baseline laboratory assessments were excluded; N=525 for Blood Creatinine, AST, ALT, Blood Bilirubin, Blood Alkaline Phosphatase and Hemoglobin; N=491 for Blood Creatine Phosphokinase.
[#] Blood triglycerides data available from study NP28761, n=98
[&] Uric acid data available from study BO40336, n=128.

2.6.2 Postmarketing Experience
The adverse drug reactions of increased alkaline phosphatase, hemolytic anemia and hypertriglyceridemia were reported with Alecensa in the post-marketing period as well as during clinical trials (*see section 2.6.1 Clinical Trials)*.

2.7 Overdose
There is no experience with overdosage across clinical trials. Patients who experience overdose should be closely supervised and supportive care instituted. There is no specific antidote for overdose with Alecensa.

2.8 Interactions with other Medicinal Products and other Forms of Interaction
Effects of alectinib on other drugs
CYP substrates
In vitro studies indicate that neither alectinib nor its major active metabolite (M4) inhibits CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant concentrations. Alectinib and M4 show weak time-dependent inhibition of CYP3A4. *In vitro*, alectinib exhibits a weak induction potential of CYP3A4 and CYP2B6 at clinical concentrations.
Results from a clinical drug-drug interaction study in ALK-positive NSCLC patients demonstrated that multiple doses of alectinib had no influence on the exposure of midazolam, a sensitive CYP3A substrate. Therefore, no dose adjustment is required for co-administered CYP3A substrates.
Although *in vitro* studies indicate that alectinib is an inhibitor of CYP2C8, physiologically based pharmacokinetic (PBPK) modeling supports that at clinically relevant concentrations alectinib does not have the potential to increase plasma concentrations of co-administered substrates of CYP2C8.

P-gp and BCRP substrates
In vitro, alectinib and M4 are inhibitors of the efflux transporters P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (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). When alectinib is co-administered with P-gp or BCRP substrates with narrow therapeutic index (e.g. digoxin, dabigatran, methotrexate), appropriate monitoring is recommended.

Effects of other drugs on alectinib
Based on *in vitro* data, CYP3A4 is the primary enzyme mediating the metabolism of both alectinib and its major active metabolite M4, and CYP3A contributes to 40%-50% of total hepatic metabolism. M4 has shown similar *in vitro* potency and activity to alectinib against ALK.

CYP3A inducers
Co-administration of multiple oral doses of 600 mg rifampicin once daily, a strong 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-gp. Alectinib and M4 are not substrates of 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

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS
3.1 Pharmacodynamic Properties
3.1.1 Mechanism of Action
Alectinib is a highly selective and potent ALK and RET tyrosine kinase inhibitor. In nonclinical studies, inhibition of ALK tyrosine kinase activity led to blockage of downstream signalling pathways including STAT 3 and PI3K/AKT and induced tumor cell death (apoptosis).
Alectinib demonstrated *in vitro* and *in vivo* activity against mutant forms of the ALK enzyme, including mutations responsible for resistance to crizotinib. The major metabolite of alectinib (M4) has shown similar *in vitro* potency and activity.
Based on nonclinical data, alectinib is not a substrate of p-glycoprotein (P-gp) or Breast Cancer Resistance Protein (BCRP), which are both efflux transporters in the blood brain barrier, and is therefore able to distribute into and be retained within the central nervous system. Alectinib induced tumor regression in nonclinical mouse xenograft models, including anti-tumor activity in the brain, and prolonged survival in intracranial tumor animal models.

3.1.2 Clinical / Efficacy Studies
Adjuvant Treatment of Resected ALK-Positive Non-Small Cell Lung Cancer
The efficacy of Alecensa for the adjuvant treatment of patients with ALK-positive NSCLC following complete tumor resection was established in a global randomized Phase III open-label clinical trial (BO40336; ALINA). Eligible patients were required to have Stage IB (tumors ≥ 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 tumor resection. Randomization 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 unacceptable 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 randomization 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 summarized in Table 5, and Figure 1 and Figure 2.

Table 5: Investigator Assessed DFS Results in ALINA

Efficacy Parameter	Stage II-IIIA Population		ITT Population	
	Alecensa N=116	**Chemo-therapy N=115**	**Alecensa N=130**	**Chemo-therapy 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

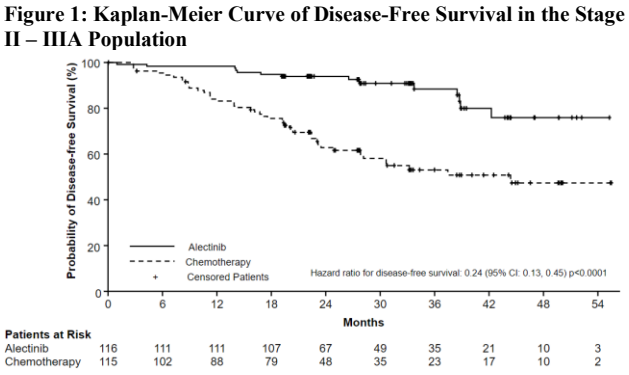
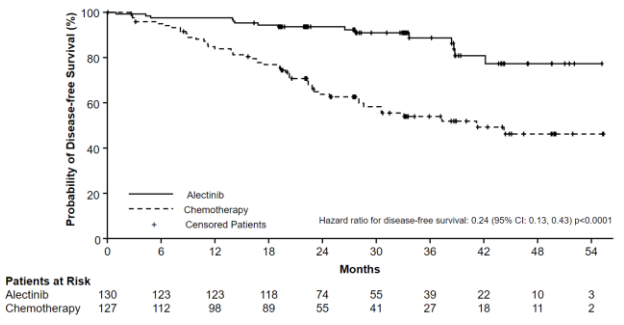


Figure 2: Kaplan-Meier Curve of Disease-Free Survival in the ITT Population



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 Non-Small Cell Lung Cancer

Treatment-naïve patients

The safety and efficacy of Alecensa were studied in a global randomized Phase III open label clinical trial (BO28984) in ALK-positive NSCLC patients who were treatment naïve. Central testing for ALK protein expression positivity of tissue samples from all patients by Ventana anti-ALK (D5F3) immunohistochemistry (IHC) was required before randomization into the study.

A total of 303 patients were included in the Phase III trial, 151 patients randomized to the crizotinib arm and 152 patients randomized to the Alecensa arm receiving Alecensa orally, at the recommended dose of 600 mg twice daily.ECOG PS (0/1 vs. 2), race (Asian vs. non-Asian), and CNS metastases at baseline (yes vs. no) were stratification factors for randomization. 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 PS 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 summarized in Table 6 and the Kaplan-Meier curves for investigator and IRC-assessed PFS are shown in Figures 3 and 4. Additionally, the Kaplan-Meier plot of overall survival from the final OS analysis is presented in Figure 5.

Table 6: Summary of efficacy results from study BO28984

	Crizotinib N=151	Alecensa N=152
Median duration of follow-up (months)‡	23.3 (range 0.3 – 123.5)	53.5 (range 0.5 – 126.8)
Primary Efficacy Parameter		
PFS (INV) † Number of patients with event n (%) Median (months) [95% CI]	102 (68%) 11.1 [9.1; 13.1]	62 (41%) NE [17.7; NE]
HR [95% CI] Stratified log-rank p-value	0.47 [0.34, 0.65] p <0.0001	
Secondary efficacy parameters		
PFS (IRC)* † Number of patients with event n (%) Median (months) [95% CI]	92 (61%) 10.4 [7.7; 14.6]	63 (41%) 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]	73 (48.3%) 54.2 [34.6; 75.6]	76 (50%) 81.1 [62.3; NE]
HR [95% CI]	0.78 [0.56; 1.08]	
Duration of response (INV)‡ Median (months) 95 % CI	N=115 11.1 [7.9; 13.0]	N=126 42.3 [31.3; 51.3]
CNS-ORR in patients with measurable CNS metastases at baseline† CNS responders n (%) [95% CI]	N=22 11 (50.0%) [28.2; 71.8]	N=21 17 (81.0%) [58.1; 94.6]
CNS-CR n (%)	1 (5%)	8 (38%)
CNS-DOR , median (months) 95% CI	5.5 [2.1, 17.3]	17.3 [14.8, NE]
CNS-ORR in patients with measurable and non-measurable CNS metastases at baseline (IRC)† CNS responders n (%) [95% CI]	N=58 15 (25.9%) [15.3%; 39.0%]	N=64 38 (59.4%) [46.4%; 71.5%]
CNS-CR n (%)	5 (9%)	29 (45%)
CNS-DOR , median (months) 95% CI	3.7 [3.2, 6.8]	NE [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

† Data from primary analysis

‡ Data from final OS analysis, which was conducted after 149 deaths had occurred

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 BO28984

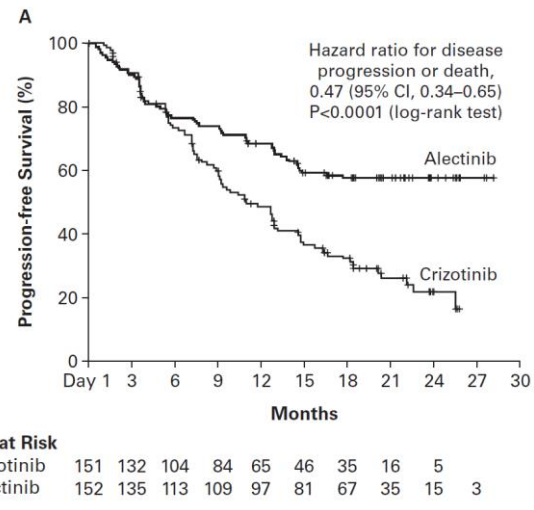


Figure 4: Kaplan Meier Plot of IRC Assessed PFS in BO28984

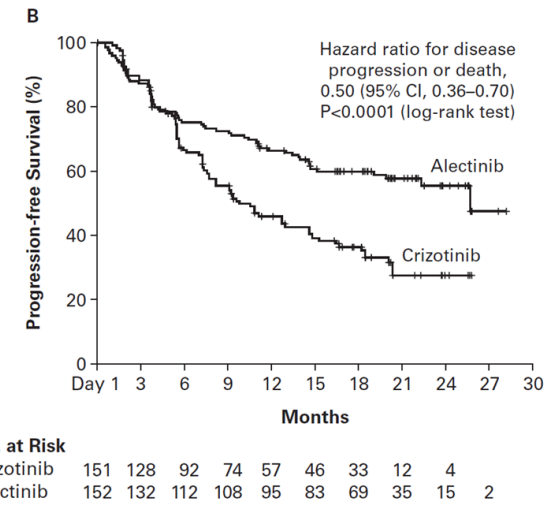
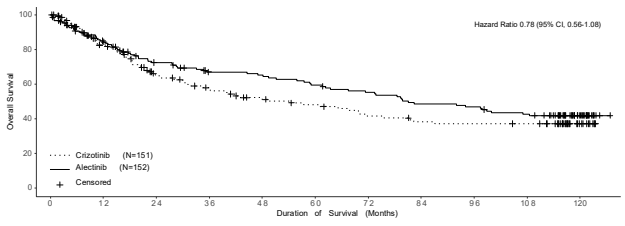


Figure 5: Kaplan Meier Plot of Overall Survival in BO28984



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 (NP28761 and NP28673).

Study NP28761 was a Phase I/II single-arm, multi-center 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 Objective Response Rate (ORR) as per central Independent Review Committee (IRC) assessment using Response Evaluation Criteria in Solid Tumors (RECIST) version 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 in 94% of patients tumors 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 7: Summary of efficacy from NP28761 study

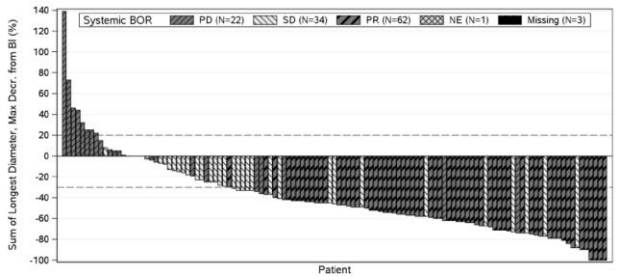
	NP28761 Alecensa 600 mg twice daily N=87
Median duration of follow-up (months)	17 (range 1 – 29)
Primary Efficacy Parameters	
ORR (IRC) in ITT population Responders N (%) [95% CI]	N = 87 37 (42.5%) [32.0%, 53.6%]
ORR (IRC) in RE population Responders N (%) [95% CI]	N = 67 [a] 35 (52.2%) [39.7%, 64.6%]
Secondary Efficacy Parameters	
DOR (IRC) in ITT population Number of patients with events N (%) Median (months) [95% CI]	N = 37 20 (54.1%) 14.9 [7.5, NE]
DOR (IRC) in RE population Number of patients with events N (%) Median (months)	N = 35 20 (57.1%) 14.9

[95% CI]	[6.9, NE]
PFS (IRC) Number of patients with events N (%) Median duration (months) [95% CI]	N = 87 58 (66.7) 8.2 [6.3, 12.6]
Exploratory Efficacy Parameters	
DCR (IRC) in ITT population[b] CR+PR+SD[c] [95% CI]	N = 87 72 (82.8%) [73.2%, 90.0%]
DCR (IRC) in RE Population[b] CR+PR+SD[c] [95% CI]	N = 67[a] 53 (79.1%) [67.4%, 88.1%]

CI = confidence interval; CR=complete response; DOR = duration of response; DCR = disease control rate; IRC = independent review committee; NE = not estimable; ORR = Objective Response Rate; PR=partial response; PFS = progression free survival RE = response evaluable; SD = stable disease
[a] 20 patients did not have measurable disease at baseline according to the IRC and were not included in the IRC response evaluable population.
[b] Exploratory analysis defined after database lock
[c] DCR calculated including all patients who achieved a Best Overall Response (BOR) of SD (minimum duration of 5 weeks as per IRC Charter)

As shown in the waterfall plot in Figure 6, most patients experienced tumour shrinkage of their defined target lesions, as assessed by the IRC according to RECIST 1.1.

Figure 6: Waterfall plot of target lesions sum of longest diameters best change from baseline shaded by best overall response (IRC) from NP28761 study



BOR= Best overall response, PD = progressive disease, SD = stable disease, PR = partial response, NE = not estimable.

Quality of life (QoL)
Of the QoL items analysed (QLQ-C30 and QLQ-LC13), clinically meaningful improvements (change from baseline of ≥10 points) were observed in the Global Health Status, Emotional Functioning, Social Functioning, Fatigue, and Pain subscales.
Study NP28673 was a Phase I/II single-arm, international, multi-center 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 ORR as per central IRC assessment using RECIST 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 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 in 96% of patients tumors 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.

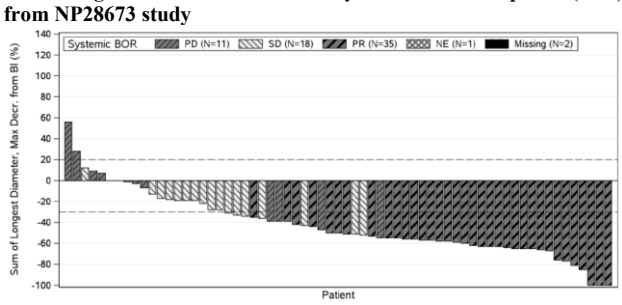
Table 8: Summary of efficacy from NP28673 study

	NP28673 Alecensa 600 mg twice daily N=138
Median duration of follow-up (months)	21 (range 1 – 30)
Primary Efficacy Parameters	
ORR (IRC) in ITT population Responders N (%) [95% CI]	N = 138 62 (44.9%) [36.5%, 53.6%]
ORR (IRC) in RE population Responders N (%) [95% CI]	N=122 [a] 62 (50.8%) [41.6%, 60.0%]
ORR (IRC) in Patients Pre-Treated with Chemotherapy in ITT population Responders N (%) [95% CI]	N = 110 43 (39.1%) [29.9%, 48.9%]
ORR (IRC) in Patients Pre-Treated with Chemotherapy in RE population Responders N (%) [95% CI]	N = 96 43 (44.8%) [34.6%, 55.3%]
Secondary Efficacy Parameters	
DOR (IRC) in ITT population Number of patients with events N (%) Median (months) [95% CI]	N = 62 36 (58.1%) 15.2 [11.2, 24.9]
DOR (IRC) in RE population Number of patients with events N (%) Median (months) [95% CI]	N = 62 36 (58.1%) 15.2 [11.2, 24.9]
PFS (IRC) Number of patients with events N (%) Median duration (months) [95% CI]	N = 138 98 (71.0%) 8.9 [5.6, 12.8]
Exploratory Efficacy Parameter	
DCR (IRC) in ITT population[b] CR+PR+SD[c] [95% CI]	N = 138 111 (80.4%) [72.8%, 86.7%]
DCR (IRC) in RE Population[b] CR + PR + SD[c] [95% CI]	N = 122[a] 96 (78.7%) [70.4%, 85.6%]

CI = confidence interval; CR=complete response; DOR = duration of response; DCR = disease control rate; IRC = independent review committee; NE = not estimable; ORR = Objective Response Rate; PFS = progression free survival; PR=partial response; RE = response evaluable; SD = stable disease
[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] Exploratory analysis defined after database lock.
[c] DCR calculated including all patients who achieved Best Overall Response (BOR) of SD (minimum duration of 5 weeks as per IRC Charter).

As shown in the waterfall plot in Figure 7:, most patients experienced tumour shrinkage of their defined target lesions, as assessed by the IRC according to RECIST 1.1.

Figure 7: Waterfall plot of target lesions sum of longest diameters best change from baseline shaded by best overall response (IRC) from NP28673 study



BOR= Best overall response, PD = progressive disease, SD = stable disease, PR = partial response, NE = not estimable.

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 the Phase II NP28761 and NP28673 is presented in the table below.

Table 9: Summary of the pooled analysis for CNS endpoints from NP28761 and NP28673 studies

CNS Parameters (NP28761 and NP28673)	**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)

In 136 patients included in the Phase II NP28761 and NP28673 with measurable and/or non-measurable CNS lesions at baseline, the CNS complete response rate was 28.7%. A CNS partial response cannot be established in non-measurable CNS lesions per RECIST. The CNS disease control rate was 86.0% [95% CI (79.1, 91.4)].

3.1.3 Immunogenicity
Not applicable

3.2 Pharmacokinetic Properties
The pharmacokinetic parameters for alectinib and its major active metabolite (M4), have been characterized in ALK-positive NSCLC patients and healthy subjects. The geometric mean (coefficient of variation %) steady-state C_{max}, C_{min} and $AUC_{0\text{-}12hr}$ for alectinib were approximately 665 ng/mL (44.3%), 572 ng/mL (47.8%) and 7430 ng*h/mL (45.7%), respectively. The geometric mean steady-state C_{max}, C_{min} and $AUC_{0\text{-}12hr}$ for M4 were approximately 246 ng/mL (45.4%), 222 ng/mL (46.6%) and 2810 ng*h/mL (45.9%), respectively.

3.2.1 Absorption
Following oral administration of 600 mg twice daily under fed conditions in ALK-positive NSCLC patients, alectinib was rapidly absorbed reaching T_{max} after approximately 4 to 6 hours.
Alectinib steady-state is reached by Day 7 with continuous 600 mg twice daily dosing and remains stable thereafter. The geometric mean accumulation ratio estimated by population PK analysis for the twice-daily 600 mg regimen is 5.6. Population PK analysis supports dose proportionality for alectinib across the dose range of 300 to 900 mg under fed conditions.
The absolute bioavailability of alectinib was 36.9% (90% CI: 33.9%, 40.3%) under fed conditions in healthy subjects.
Following a single oral administration of 600 mg with a high-fat, high-calorie meal, exposure increased by 3-fold relative to fasted conditions (geometric mean ratio [90% CI] of combined alectinib and M4: C_{max}: 3.31 [2.79–3.93], AUC_{inf}: 3.11 [2.73–3.55].

3.2.2 Distribution
Alectinib and its major metabolite 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 i.v. administration was 475 L, indicating extensive distribution into tissues. The apparent volume of distribution is 4,016 L for alectinib and 10,093 L for M4

3.2.3 Metabolism
In vitro metabolism studies showed that CYP3A4 is the main CYP isozyme mediating alectinib and its major metabolite M4 metabolism, and is estimated to contribute 40% – 50% of alectinib metabolism in human hepatocytes. Results from the human mass balance study demonstrated that alectinib and M4 were the main circulating moieties in plasma with alectinib and M4 together constituting approximately 76% of the total radioactivity in plasma. The geometric mean metabolite/parent ratio at steady state is 0.399.

3.2.4 Elimination
Following administration of a single dose of ^{14}C-labeled alectinib administered orally to healthy subjects the majority of radioactivity was excreted in feces (mean recovery 97.8%, range 95.6%-100%) with minimal excretion in urine (mean recovery 0.46%, range 0.30%-0.60%). In feces, 84% and 5.8% of the dose was excreted as unchanged alectinib or M4, respectively.
Based on a population PK analysis, the apparent clearance (CL/F) of alectinib was 81.9 L/hour. The geometric mean of the individual elimination half-life estimates for alectinib was 32.5 hours. The corresponding values for M4 were 217 L/hour and 30.7 hours, respectively.

3.2.5 Pharmacokinetics in Special Populations
Pediatric population
No studies have been conducted to investigate the pharmacokinetics of Alecensa in this population.

Geriatric population
Age does not have an effect on Alecensa exposure.

Renal impairment
Negligible amounts of alectinib and the active metabolite M4 are excreted unchanged in urine (<0.2% of the dose). Data obtained in patients with mild and moderate renal impairment show that the pharmacokinetics of alectinib are not significantly affected in renal impairment. No formal pharmacokinetic study has been conducted and no population PK data was collected in patients with severe renal impairment, however, since alectinib elimination via the kidney is negligible, no dose adjustment is required in renal impairment.

Hepatic impairment
As elimination of alectinib is predominantly through metabolism in the liver, hepatic impairment may increase the plasma concentration of alectinib and/or its major active metabolite M4. Based on a population pharmacokinetic analysis, alectinib and M4 exposures were similar in patients with mild hepatic impairment (baseline total bilirubin less than or equal to ULN and baseline AST greater than ULN or baseline total bilirubin greater than 1.0 to 1.5 times ULN and any baseline AST) and normal hepatic function (total bilirubin less than or equal to ULN and AST less than or equal to ULN).
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]). The subjects in the Child Pugh B group however did in general not suffer from abnormal bilirubin, albumin or prothrombin time, indicating that they may not be fully representative of moderately hepatically impaired subjects with decreased metabolic capacity.
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]).
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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).

3.3 Nonclinical Safety
3.3.1 Carcinogenicity
No carcinogenicity studies have been performed to establish the carcinogenic potential of Alecensa.

3.3.2 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 (CHL) 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.

3.3.3 Impairment of Fertility
No fertility studies in animals have been performed to evaluate the effect of Alecensa. 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.

3.3.4 Reproductive toxicity
In animal studies, a maternal dose of alectinib equivalent to 2.7 times the recommended human dose of 600 mg twice daily (based on AUC), caused embryo-fetal loss (miscarriage) in pregnant rabbits. The same equivalent dose given to pregnant rats resulted in small fetuses with retarded ossification and minor abnormalities of the organs.

3.3.5 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.
Target organs in both rat and monkey at clinically relevant exposures in the repeat-dose toxicology studies included, but were not limited to the erythroid system, gastrointestinal tract and hepatobiliary system.
Abnormal erythrocyte morphology was observed at exposures equal or greater than 10-60% the human exposure by AUC at the recommended dose. Proliferative zone extension in GI mucosa in both species was observed at exposures equal to or greater than 20-120% of the human AUC exposure at the recommended dose. Increased hepatic alkaline phosphatase (ALP) and direct bilirubin as well as vacuolation/degeneration/necrosis of bile duct epithelium and enlargement/focal necrosis of hepatocytes was observed in rats and/or monkeys at exposures equal to or greater than 20-30% of the human exposure by AUC at the recommended dose.
A mild hypotensive effect has been observed in monkeys at around clinically relevant exposures.
Alectinib crossed the blood-brain barrier in rats and was retained within brain tissue with a CNS-to-plasma radio-concentration ratio ranging from 0.9 to 1.5 at 24 hrs post-dose.

4. PHARMACEUTICAL PARTICULARS

4.1 Storage
Shelf life
As registered locally

Storage
As registered locally

Keep container tightly closed, protect from light and moisture.

This medicine should not be used after the expiry date (EXP) shown on the pack.

4.2 Special Instructions for Use, Handling and Disposal
Disposal of unused/expired medicines
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

4.3 Packs
Capsules 150 mg 224

Medicine: Keep out of reach of children

Current at February 2026

F. Hoffmann-La Roche Ltd, Basel, Switzerland