▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

ALUNBRIG® (BRIGATINIB)

1 NAME OF THE MEDICINE

ALUNBRIG (brigatinib)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ALUNBRIG 30 mg film-coated tablets

Each film-coated tablet contains 30 mg of brigatinib. Excipient with known effect: Each film-coated tablet contains 56 mg of lactose monohydrate.

ALUNBRIG 90 mg film-coated tablets

Each film-coated tablet contains 90 mg of brigatinib. Excipient with known effect: Each film-coated tablet contains 168 mg of lactose monohydrate.

ALUNBRIG 180 mg film-coated tablets

Each film-coated tablet contains 180 mg of brigatinib. Excipient with known effect: Each film-coated tablet contains 336 mg of lactose monohydrate.

For the full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

ALUNBRIG 30 mg film-coated tablets

Round, white to off-white with debossed “U3” on one side and plain on the other side.

ALUNBRIG 90 mg film-coated tablets

Oval, white to off-white with debossed “U7” on one side and plain on the other side.

ALUNBRIG 180 mg film-coated tablets

Oval, white to off-white with debossed “U13” on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ALUNBRIG is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC).

4.2 DOSE AND METHOD OF ADMINISTRATION

ALK-positive NSCLC status should be known prior to initiation of ALUNBRIG therapy. A validated ALK assay is necessary for the selection of ALK-positive NSCLC patients.

Treatment with ALUNBRIG should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

The recommended starting dose of ALUNBRIG is 90 mg once daily for the first 7 days, then 180 mg once daily. Treatment should continue as long as clinical benefit is observed.

If a dose of ALUNBRIG is missed, or vomiting occurs after taking a dose, an additional dose should not be administered and the next dose of ALUNBRIG should be taken at the scheduled time.

Dose Adjustments

Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. ALUNBRIG dose reduction levels are summarised in Table 1.

Table 1: Recommended ALUNBRIG Dose Reduction Levels

Dose	**Dose reduction levels**		
	First	**Second**	**Third**
90 mg once daily (first 7 days)	reduce to 60 mg once daily	permanently discontinue	Not applicable
180 mg once daily	reduce to 120 mg once daily	reduce to 90 mg once daily	reduce to 60 mg once daily

Permanently discontinue ALUNBRIG if patient is unable to tolerate the 60 mg once daily dose.

If ALUNBRIG is interrupted for 14 days or longer for reasons other than adverse reactions, treatment should be resumed at 90 mg once daily for 7 days before increasing to the previously tolerated dose.

Recommendations for dose modifications of ALUNBRIG for the management of adverse reactions are summarised in Table 2.

Table 2: Recommended ALUNBRIG dose modifications for adverse reactions

Adverse reaction	**Severity***	**Dose modification**
Interstitial lung disease (ILD)/pneumonitis	Grade 1	• If new pulmonary symptoms occur during the first 7 days of treatment, withhold ALUNBRIG until recovery to baseline, then resume at the same dose and do not escalate to 180 mg if ILD/pneumonitis is suspected. • If new pulmonary symptoms occur after the first 7 days of treatment, withhold ALUNBRIG until recovery to baseline, then resume at the same dose. • If ILD/pneumonitis recurs, permanently discontinue ALUNBRIG.
	Grade 2	• If new pulmonary symptoms occur during the first 7 days of treatment, withhold ALUNBRIG until recovery to baseline. Resume at the next lower dose (Table 1) and do not dose escalate if ILD/pneumonitis is suspected. • If new pulmonary symptoms occur after the first 7 days of treatment, withhold ALUNBRIG until recovery to baseline. If ILD/pneumonitis is suspected, resume at the next lower dose (Table 1); otherwise, resume at same dose. • If ILD/pneumonitis recurs, permanently discontinue ALUNBRIG.
	Grade 3 or 4	• ALUNBRIG should be permanently discontinued.
Hypertension	Grade 3 hypertension	• ALUNBRIG should be withheld until hypertension has recovered to Grade ≤ 1

Adverse reaction	Severity*	Dose modification
	(SBP ≥ 160 mmHg or DBP ≥ 100 mmHg, medical intervention indicated, more than one anti-hypertensive medicinal product, or more intensive therapy than previously used indicated)	(SBP <140 mmHg and DBP <90 mmHg), then resumed at the same dose. • If Grade 3 hypertension recurs, ALUNBRIG should be withheld until hypertension has recovered to Grade ≤ 1 then resumed at the next lower dose level per Table 1 or permanently discontinued
	Grade 4 hypertension (life threatening consequences, urgent intervention indicated)	• ALUNBRIG should be withheld until hypertension has recovered to Grade ≤ 1 (SBP <140 mmHg and DBP <90 mmHg), then resumed at the next lower dose level per Table 1 or permanently discontinued • If Grade 4 hypertension recurs, ALUNBRIG should be permanently discontinued.
Bradycardia (Heart Rate less than 60 bpm)	Symptomatic bradycardia	• ALUNBRIG should be withheld until recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above. • If a concomitant medicinal product known to cause bradycardia is identified and discontinued, or its dose is adjusted, ALUNBRIG should be resumed at the same dose upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above. • If no concomitant medicinal product known to cause bradycardia is identified, or if contributing concomitant medicinal product is not discontinued or dose modified, ALUNBRIG should be resumed at the next lower dose level per Table 1 upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above.
	Bradycardia with life-threatening consequences, urgent intervention indicated	• If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, ALUNBRIG should be resumed at the next lower dose level per Table 1 upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above, with frequent monitoring as clinically indicated. • ALUNBRIG should be permanently discontinued if no contributing concomitant medicinal product is identified. • ALUNBRIG should be permanently discontinued in case of recurrence.

Adverse reaction	Severity*	Dose modification
Elevation of Creatine Phosphokinase (CPK)	Grade 3 or 4 elevation of CPK (>5.0 × ULN) with Grade ≥ 2 muscle pain or weakness	• ALUNBRIG should be withheld until recovery to Grade ≤ 1 (≤2.5 × ULN) elevation of CPK or to baseline, then resumed at the same dose. • If Grade 3 or 4 elevation of CPK recurs with Grade ≥ 2 muscle pain or weakness, ALUNBRIG should be withheld until recovery to Grade ≤ 1 (≤2.5 × ULN) elevation of CPK or to baseline, then resumed at the next lower dose level per Table 1.
Elevation of lipase or amylase	Grade 3 elevation of lipase or amylase (>2.0 × ULN)	• ALUNBRIG should be withheld until recovery to Grade ≤ 1 (≤1.5 × ULN) or to baseline, then resumed at same dose. • If Grade 3 elevation of lipase and amylase recurs, ALUNBRIG should be withheld until recovery to Grade ≤ 1 (≤1.5 × ULN) or to baseline, then resumed at the next lower dose level per Table 1.
	Grade 4 elevation of lipase or amylase (>5.0 x ULN)	• ALUNBRIG should be withheld until recovery to Grade ≤ 1 (≤1.5 × ULN), then resumed at the next lower dose level per Table 1.
Elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST)	Grade ≥ 3 elevation (> 5.0 × ULN) of either ALT or AST with bilirubin ≤ 2 × ULN	• ALUNBRIG should be withheld until recovery to baseline or ≤ 3 × ULN, then resumed at next lower dose per Table 1.
	Grade ≥ 2 elevation (> 3 × ULN) of ALT or AST with concurrent total bilirubin elevation > 2 × ULN in the absence of cholestasis or haemolysis	• ALUNBRIG should be permanently discontinued.
Hyperglycaemia	For Grade 3 (greater than 250 mg/dL or 13.9 mmol/L) or greater	• If adequate hyperglycaemic control cannot be achieved with optimal medical management, ALUNBRIG should be withheld until adequate hyperglycaemic control is achieved. Upon recovery, ALUNBRIG may either be resumed at the next lower dose per Table 1 or permanently discontinued.
Visual Disturbance	Grade 2 or 3	• ALUNBRIG should be withheld until recovery to Grade 1 or baseline, then resumed at the next lower dose level per Table 1.
	Grade 4	• ALUNBRIG should be permanently discontinued.

Adverse reaction	Severity*	Dose modification
Other adverse reactions	Grade 3	• ALUNBRIG should be withheld until recovery to baseline, then resumed at the same dose level. • If the Grade 3 event recurs, ALUNBRIG should be withheld until recovery to baseline, then resumed at the lower dose level as per Table 1 or permanently discontinued.
	Grade 4	• ALUNBRIG should be withheld until recovery to baseline, then resumed at the next lower dose level as per Table 1. • If the Grade 4 event recurs, ALUNBRIG should be withheld until recovery to baseline, then resumed at the next lower dose level as per Table 1 or permanently discontinued.
bpm = beats per minute; CPK = Creatine Phosphokinase; DBP = diastolic blood pressure; SBP = systolic blood pressure; ULN = upper limit of normal		

*Graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4).

Special Patient Populations

Elderly

The limited data on the safety and efficacy of ALUNBRIG in patients aged 65 years and older suggest that a dose adjustment is not required in elderly patients. There are limited data on patients over 85 years of age.

Paediatrics

The safety and efficacy of ALUNBRIG in patients less than 18 years of age have not been established. No data are available.

Renal impairment

No dose adjustment of ALUNBRIG is required for patients with mild or moderate renal impairment (estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2). The dose of brigatinib should be reduced by approximately 50% (i.e., from 180 mg to 90 mg, or from 90 mg to 60 mg) for patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) (see section 5.2 Pharmacokinetic Properties). These dosing recommendations for patients with severe renal impairment are based on the results of a single-dose pharmacokinetic study. Patients should be closely monitored as the safety of brigatinib has not been studied in patients with severe renal impairment.

Hepatic impairment

No dose adjustment of ALUNBRIG is required for patients with mild hepatic impairment (Child-Pugh class A) or moderate hepatic impairment (Child-Pugh class B). The dose of brigatinib should be reduced by approximately 40% (i.e., from 180 mg to 120 mg, 120 mg to 90 mg, or from 90 mg to 60 mg) for patients with severe hepatic impairment (Child-Pugh class C) (see section 5.2 Pharmacokinetic Properties). These dosing recommendations are based on the results of a single-dose pharmacokinetic study. Patients should be closely monitored as the safety of brigatinib has not been studied in patients with hepatic impairment.

Method of Administration

ALUNBRIG is for oral use. The tablets should be swallowed whole and with water. Do not crush or chew tablets. ALUNBRIG may be taken with or without food.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 List of excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

PULMONARY ADVERSE REACTIONS

Severe, life-threatening, and fatal pulmonary adverse reactions, including those with features consistent with ILD/pneumonitis, can occur in patients treated with ALUNBRIG [see section 4.8 Adverse Effects (Undesirable Effects)]. Most pulmonary adverse reactions were observed within the first 7 days of treatment. Grade 1-2 pulmonary adverse reactions resolved with interruption of treatment or dose modification. Increased age and shorter interval (less than 7 days) between the last dose of crizotinib and the first dose of ALUNBRIG were independently associated with an increased rate of these pulmonary adverse reactions. These factors should be considered when initiating treatment with ALUNBRIG. Patients with a history of ILD or drug-induced pneumonitis were excluded from the pivotal trial. Some patients experienced pneumonitis later in treatment with ALUNBRIG. Patients should be monitored for and instructed to report any new or worsening respiratory symptoms (e.g., dyspnoea, cough, etc.), particularly in the first week of treatment. Evidence of pneumonitis in any patient with worsening respiratory symptoms should be promptly investigated. If pneumonitis is suspected, ALUNBRIG should be withheld, and the patient evaluated for other causes of symptoms (e.g., pulmonary embolism, tumour progression, and infectious pneumonia) and dosing modified accordingly (see section 4.2 Dose and Method of Administration).

HYPERTENSION

Hypertension has occurred in patients treated with ALUNBRIG [see section 4.8 Adverse Effects (Undesirable Effects)]. Blood pressure should be monitored regularly during treatment with ALUNBRIG. Hypertension should be treated according to standard guidelines to control blood pressure. For severe hypertension (≥ Grade 3), ALUNBRIG should be withheld until hypertension has recovered to Grade 1 or to baseline. The dose should be modified accordingly (see section 4.2 Dose and Method of Administration).

BRADYCARDIA

Bradycardia has occurred in patients treated with ALUNBRIG [see section 4.8 Adverse Effects (Undesirable Effects)]. Heart rate and blood pressure should be monitored regularly. Caution should be exercised when administering ALUNBRIG in combination with other agents known to cause bradycardia. Heart rate should be monitored more frequently in patients if concomitant use of a medicinal product known to cause bradycardia cannot be avoided. If symptomatic bradycardia occurs, treatment with ALUNBRIG should be withheld and concomitant medications known to cause bradycardia should be evaluated. Upon recovery, the dose should be modified accordingly (see section 4.2 Dose and Method of Administration). In case of life-threatening bradycardia, if no contributing concomitant medication is identified, or in case of recurrence, treatment with ALUNBRIG should be discontinued (see section 4.2 Dose and Method of Administration).

VISUAL DISTURBANCE

Visual disturbance adverse reactions have occurred in patients treated with ALUNBRIG [see section 4.8 Adverse Effects (Undesirable Effects)]. Patients should be advised to report any visual symptoms. For new or worsening severe visual symptoms, an ophthalmologic evaluation and dose reduction should be considered (section 4.2 Dose and Method of Administration).

CREATINE PHOSPHOKINASE (CPK) ELEVATION

Elevations of CPK have occurred in patients treated with ALUNBRIG [see section 4.8 Adverse

Effects (Undesirable Effects)]; the pathology resulting in CPK elevation is unknown. Significant myopathies (such as rhabdomyolysis or cardiomyopathies) were not observed in the clinical trials. However, the rare occurrence of significant myopathies cannot be ruled out. Patients should be advised to report any unexplained muscle pain, tenderness, or weakness. CPK levels should be monitored regularly during ALUNBRIG treatment. Based on the severity of the CPK elevation, and if associated with muscle pain or weakness, treatment with ALUNBRIG should be withheld, and the dose modified accordingly (see section 4.2 Dose and Method of Administration).

ELEVATIONS OF PANCREATIC ENZYMES

Elevations of amylase and lipase have occurred in patients treated with ALUNBRIG [see section 4.8 Adverse Effects (Undesirable Effects)]. Lipase and amylase should be monitored regularly during treatment with ALUNBRIG. Based on the severity of the laboratory abnormalities, treatment with ALUNBRIG should be withheld, and the dose modified accordingly (see section 4.2 Dose and Method of Administration).

HEPATIC ENZYME ELEVATION'

Elevations of hepatic enzymes (aspartate aminotransferase, alanine aminotransferase) and bilirubin have occurred in patients treated with ALUNBRIG (see section 4.8). Liver function, including AST, ALT and total bilirubin should be assessed prior to the initiation of ALUNBRIG and then every 2 weeks during the first 3 months of treatment. Thereafter, monitoring should be performed periodically. Based on the severity of the laboratory abnormalities, treatment should be withheld, and the dose modified accordingly (see section 4.2 Dose and Method of Administration).

HYPERGLYCAEMIA

Elevations of serum glucose have occurred in patients treated with ALUNBRIG [see section 4.8 Adverse Effects (Undesirable Effects)]. Fasting serum glucose should be assessed prior to initiation of ALUNBRIG and monitored periodically thereafter. Antihyperglycaemic medications should be initiated or optimised as needed. If adequate hyperglycaemic control cannot be achieved with optimal medical management, ALUNBRIG should be withheld until adequate hyperglycaemic control is achieved; upon recovery reducing the dose of ALUNBRIG as described in section 4.2 Dose and Method of Administration may be considered or ALUNBRIG may be permanently discontinued.

PHOTOSENSITIVITY

Photosensitivity to sunlight has occurred in patients treated with brigatinib (see section 4.8 Adverse Effects (Undesirable Effects)). Patients should be advised to avoid prolonged sun exposure while taking brigatinib, and for at least 5 days after discontinuation of treatment. When outdoors, patients should be advised to wear a hat and protective clothing, and to use a broad-spectrum Ultraviolet A (UVA/Ultraviolet B (UVB) sunscreen and lip balm (SPF ≥30) to help protect against potential sunburn. For severe photosensitivity reactions (≥ Grade 3), brigatinib should be withheld until recovery to baseline. The dose should be modified accordingly (see section 4.2 Dose and Method of Administration).

FERTILITY

Women of childbearing potential should be advised to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months following the final dose. Men with female partners of childbearing potential should be advised to use effective contraception during treatment and for at least 3 months after the last dose of ALUNBRIG (see section 4.6 Fertility, Pregnancy and Lactation).

USE IN THE ELDERLY

See section 4.2 Dose and Method of Administration.

PAEDIATRIC USE

See section 4.2 Dose and Method of Administration.

EFFECTS ON LABORATORY TESTS

See section 4.4 Special Warnings and Precautions for Use and section 4.8 Adverse Effects (Undesirable Effects).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

AGENTS THAT MAY INCREASE BRIGATINIB PLASMA CONCENTRATIONS

CYP3A Inhibitors

The concomitant use of strong CYP3A inhibitors with ALUNBRIG, including but not limited to certain antivirals (e.g., indinavir, nelfinavir, ritonavir, saquinavir), macrolide antibiotics (e.g., clarithromycin, telithromycin, troleandomycin), antifungals (e.g., ketoconazole, voriconazole), and nefazodone should be avoided. If concomitant use of strong CYP3A inhibitors cannot be avoided, the dose of ALUNBRIG should be reduced by approximately 50% (i.e., from 180 mg to 90 mg, or from 90 mg to 60 mg). After discontinuation of a strong CYP3A inhibitor, ALUNBRIG should be resumed at the dose that was tolerated prior to the initiation of the strong CYP3A inhibitor. *In vitro* studies demonstrated that brigatinib is a substrate of CYP3A4/5. Coadministration of multiple 200 mg twice daily doses of itraconazole, a strong CYP3A inhibitor, with a single 90 mg brigatinib dose increased brigatinib C_{max} by 21%, $AUC_{0\text{-}INF}$ by 101% (2-fold), and $AUC_{0\text{-}120}$ by 82% (<2-fold), relative to a 90 mg brigatinib dose administered alone.

The concomitant use of moderate CYP3A inhibitors (e.g., diltiazem and verapamil) with brigatinib should be avoided. If concomitant use of moderate CYP3A inhibitors cannot be avoided, the dose of brigatinib should be reduced by approximately 40% (i.e., from 180 mg to 120 mg, 120 mg to 90 mg, or from 90 mg to 60 mg). After discontinuation of a moderate CYP3A inhibitor, brigatinib should be resumed at the dose that was tolerated prior to the initiation of the moderate CYP3A inhibitor.

Grapefruit or grapefruit juice may also increase plasma concentrations of brigatinib and should be avoided.

CYP2C8 Inhibitors

No dose adjustment is required for ALUNBRIG during coadministration with strong CYP2C8 inhibitors. *In vitro* studies demonstrated that brigatinib is a substrate of CYP2C8. Coadministration of multiple 600 mg twice daily doses of gemfibrozil, a strong CYP2C8 inhibitor, with a single 90 mg brigatinib dose decreased brigatinib C_{max} by 41%, $AUC_{0\text{-}INF}$ by 12%, and $AUC_{0\text{-}120}$ by 15%, relative to a 90 mg brigatinib dose administered alone. The effect of gemfibrozil on the pharmacokinetics of brigatinib is not clinically meaningful and the underlying mechanism for the decreased exposure of brigatinib is unknown.

P-gp and BCRP Inhibitors

Brigatinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) *in vitro*. No dose adjustment is required for ALUNBRIG during coadministration with P-gp and BCRP inhibitors. Brigatinib exhibits high solubility and high permeability. Additionally, simulations from a physiologically-based pharmacokinetic model suggested that inhibition of P-gp and BCRP is not expected to result in a clinically meaningful change in the systemic exposure of brigatinib.

AGENTS THAT MAY DECREASE BRIGATINIB PLASMA CONCENTRATIONS

CYP3A Inducers

The concomitant use of strong CYP3A inducers with ALUNBRIG, including but not limited to rifampicin, carbamazepine, phenytoin, rifabutin, phenobarbital, and St. John's Wort should be avoided. Coadministration of multiple 600 mg daily doses of rifampicin, a strong CYP3A inducer, with a single 180 mg brigatinib dose decreased brigatinib C_{max} by 60%, $AUC_{0\text{-}INF}$ by 80% (5-fold), and $AUC_{0\text{-}120}$ by 80% (5-fold), relative to a 180 mg brigatinib dose administered alone. The concomitant use of moderate CYP3A inducers with ALUNBRIG, including but not limited to efavirenz, modafinil, bosentan, etravirine, and nafcillin should be avoided. Moderate CYP3A inducers may decrease the AUC of brigatinib by approximately 50% based on simulations from a physiologically-based pharmacokinetic model. If concomitant use of moderate CYP3A inducers cannot be avoided, the dose of brigatinib may be increased in 30 mg increments after 7 days of treatment with the current brigatinib dose as tolerated, up to a maximum of twice the brigatinib dose that was tolerated prior to the initiation of the moderate CYP3A inducer. After discontinuation of a moderate CYP3A inducer, brigatinib should be resumed at the dose that was tolerated prior to the initiation of the moderate CYP3A inducer.

AGENTS THAT MAY HAVE THEIR PLASMA CONCENTRATIONS ALTERED BY BRIGATINIB

CYP3A Substrates

Brigatinib reduces plasma concentrations of coadministered medicinal products that are predominantly metabolised by CYP3A. Brigatinib may also induce other enzymes and transporters (e.g., CYP2C, P-gp) via the same mechanisms responsible for induction of CYP3A (e.g., pregnane X receptor activation). *In vitro* studies in hepatocytes have shown that brigatinib is an inducer of CYP3A4. Coadministration of multiple 180 mg daily doses of brigatinib with a single 3 mg oral dose of midazolam, a sensitive CYP3A substrate, decreased midazolam C_{max} by 16%, AUC0-INF by 26%, and AUC0-last by 30%, relative to a 3 mg oral dose of midazolam administered alone.

Transporter Substrates

Brigatinib is an inhibitor of P-gp, BCRP, organic cation transporter 1 (OCT1), multidrug and toxin extrusion protein 1 (MATE1), and 2K (MATE2K) *in vitro*. Coadministration of brigatinib with substrates of P-gp, (e.g. digoxin, dabigatran, colchicine, pravastatin), BCRP (e.g., methotrexate, rosuvastatin, sulfasalazine), OCT1, MATE1, and MATE2K may increase their plasma concentrations. Patients should be closely monitored when ALUNBRIG is coadministered with substrates of these transporters with a narrow therapeutic index (e.g., digoxin, dabigatran, methotrexate).

4.6 FERTILITY, PREGNANCY AND LACTATION

EFFECTS ON FERTILITY

No human data on the effect of ALUNBRIG on fertility are available. Based on repeat dose toxicity studies in male animals, ALUNBRIG may cause reduced fertility in males. The clinical relevance of these findings to human fertility is unknown.

Testicular toxicity was observed in repeat-dose animal studies. In rats, findings included lower weight of testes, seminal vesicles and prostate gland, and testicular tubular degeneration; these effects were not reversible during the recovery period. In monkeys, findings included reduced size of testes; this effect was reversible during the recovery period. Overall, these effects on the male reproductive organs in rats and monkeys occurred at exposures as low as 0.2-times the AUC in patients at the 180 mg once daily dose. No apparent adverse effects on female reproductive organs were observed in general toxicology studies in rats and monkeys.

USE IN PREGNANCY (CATEGORY D)

ALUNBRIG may cause fetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity. There are no clinical data on the use of ALUNBRIG in pregnant women. ALUNBRIG should not be used during pregnancy unless the clinical condition of the mother requires treatment. If ALUNBRIG is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Women of childbearing age being treated with ALUNBRIG should be advised not to become pregnant and men being treated with ALUNBRIG should be advised not to father a child during treatment. Women of reproductive potential should be advised to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months following the final dose. Male patients with female partners of reproductive potential should be advised to use effective contraception during treatment and for at least 3 months after the last dose of ALUNBRIG.

In an embryofetal development study in which pregnant rats were administered daily oral doses of up to 25 mg/kg/day of brigatinib during organogenesis, dose-related skeletal (incomplete ossification, small incisors, wavy/notched/absent ribs) and visceral anomalies were observed at doses as low as 12.5 mg/kg/day (approximately 0.6 times the human exposure by AUC at 180 mg once daily). Malformations observed at 25 mg/kg/day (approximately 1.1 times the human AUC at 180 mg once daily) included anasarca (generalised subcutaneous oedema), anophthalmia (absent eyes), forelimb hyperflexion, small, short and/or bent limbs, multiple fused ribs, bent scapulae, omphalocele (intestine protruding into umbilicus), and gastroschisis (intestines protruding through a defect in the abdominal wall) along with visceral findings of moderate bilateral dilatation of the lateral ventricles.

USE IN LACTATION

It is unknown whether ALUNBRIG is excreted in human milk. Available data cannot exclude potential excretion in human milk. Breast-feeding should be stopped during treatment with ALUNBRIG.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are no data on the effect of ALUNBRIG on the ability to drive and use machines. Visual disturbance, dizziness, and fatigue have been observed in clinical trials. Patients should be advised not to drive or operate machines if they experience any of these symptoms while taking ALUNBRIG.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The adverse reactions described in this section were identified from three clinical trials:

- Study 301 (ALTA 1L): A randomised, open label, multicentre trial in patients with advanced ALK positive NSCLC who had not previously received an ALK targeted therapy. Patients were randomised in a 1:1 ratio to receive ALUNBRIG 180 mg once daily with a 7 day lead in at 90 mg once daily (N = 137) or crizotinib 250 mg orally twice daily (N = 138). The median relative dose intensity was 97% for ALUNBRIG and 99% for crizotinib.
- Study 201 (ALTA): A randomised, open label, multicentre trial in patients treated with ALUNBRIG with ALK-positive NSCLC who previously progressed on crizotinib. Patients were randomised in a 1:1 ratio to receive ALUNBRIG either 90 mg once daily continuously (90 mg regimen, N = 112) or 180 mg once daily with a 7-day lead in at 90 mg once daily (180 mg regimen, N = 110)
- Study 101: An open-label multicentre phase 1/2 dose escalation/expansion trial in patients with advanced malignancies

Across these three studies, ALK-positive NSCLC patients receiving the recommended dosing regimen had a median duration of treatment of 21.8 months.

The most common adverse reactions reported in patients (≥25%) treated with ALUNBRIG at the 180 mg regimen were increased AST (68%), increased CPK (64%), hyperglycaemia (61%),

increased lipase (54%), hyperinsulinemia (53%), diarrhoea (49%), increased ALT (49%), increased amylase (47%), anaemia (47%), nausea (40%), fatigue (40%), hypophosphataemia (39%), decreased lymphocyte count (39%), cough (38%), rash (37%), increased alkaline phosphatase (37%), increased APTT (36%), myalgia (34%), headache (33%), hypertension (30%),decreased WBC count (28%) dyspnoea (27%), and vomiting (26%).

The most common serious adverse reactions reported in 2% or more of patients at the 180 mg regimen, other than events related to neoplasm progression included pneumonia (6.9%) pneumonitis (5.5%), dyspnoea (2.9%) and pyrexia (2.2%).

Treatment-emergent adverse events (TEAE) that led to discontinuation of brigatinib occurred in 12% of patients receiving the 180 mg regimen. The most common TEAEs (occurring in ≥2 patients receiving the 180 mg regimen) other than events related to neoplasm progression, that led to brigatinib discontinuation were pneumonitis 3.3%, pneumonia 1.8% and bradycardia 0.7%.

Treatment-emergent adverse events that led to dose reduction occurred in 32.8% of patients receiving the 180 mg regimen. The TEAEs leading to dose reduction that occurred in ≥2% of patients receiving the 180 mg regimen were blood CPK increased 10.2%, lipase increased 4.7%, rash 3.3%, and amylase increased 2.9%.

Adverse reactions reported in Table 3 are listed by system organ class, preferred term and frequency. The following convention is used for the classification of the frequency of an adverse drug reaction (ADR) and is based on the Council for International Organisations of Medical Sciences (CIOMS) guidelines: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to< 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Table 3: Adverse Reactions reported in patients treated with ALUNBRIG (per Common Terminology Criteria for Adverse Events (CTCAE) version 4.03) at the 180 mg regimen (N = 274)

System organ class	Frequency category	Adverse reactions† all grades	Adverse reactions grade 3-4
Infections and infestations	Very common	Pneumonia[a, b] Upper respiratory tract infection	
	Common		Pneumonia[a]
Blood and lymphatic system disorders	Very common	Anaemia Lymphocyte count decreased APTT increased White blood cell count decreased Neutrophil count decreased	Lymphocyte count decreased
	Common	Decreased platelet count	APTT increased Anaemia
	Uncommon		Neutrophil count decreased
Metabolism and nutrition disorders	Very common	Hyperglycaemia Hyperinsulinaemia[c] Hypophosphataemia Hypomagnesaemia Hypercalcaemia Hyponatraemia Hypokalaemia Decreased appetite	

System organ class	Frequency category	Adverse reactions† all grades	Adverse reactions grade 3-4
	Common		Hypophosphataemia Hyperglycaemia Hyponatraemia Hypokalaemia Decreased appetite
Psychiatric disorders	Common	Insomnia	
Nervous system disorders	Very common	Headache[d] Peripheral neuropathy[e] Dizziness	
	Common	Memory impairment Dysgeusia	Headache[d] Peripheral neuropathy[e]
	Uncommon		Dizziness
Eye disorders	Very common	Visual Disturbance[f]	
	Common		Visual Disturbance[f]
Cardiac disorders	Common	Bradycardia[g] Electrocardiogram QT prolonged Tachycardia[h] Palpitations	Electrocardiogram QT prolonged
	Uncommon		Bradycardia[g]
Vascular disorders	Very Common	Hypertension[i]	Hypertension[i]
Respiratory, thoracic and mediastinal disorders	Very Common	Cough Dyspnoea[j]	
	Common	Pneumonitis[k]	Pneumonitis[k] Dyspnoea[h]
Gastrointestinal disorders	Very Common	Lipase increased Diarrhoea[j] Amylase increased Nausea Vomiting Abdominal pain[l] Constipation Stomatitis[m]	Lipase increased
	Common	Dry mouth Dyspepsia Flatulence	Amylase increased Nausea Abdominal pain[l] Diarrhoea
	Uncommon		Vomiting Stomatitis[m] Dyspepsia
Hepatobiliary disorders	Very Common	AST increased ALT increased Alkaline phosphatase increased	

System organ class	Frequency category	Adverse reactions† all grades	Adverse reactions grade 3-4
	Common	Blood lactate dehydrogenase increased	ALT increased AST increased Alkaline phosphatase increased
Skin and subcutaneous tissue disorders	Very common	Rash[n] Pruritus[o]	
	Common	Dry skin Photosensitivity reaction	Rash[n] Photosensitivity reaction
	Uncommon		Dry skin Pruritus[o]
Musculoskeletal and connective tissue disorders	Very common	Blood CPK increased Myalgia[p] Arthralgia	Blood CPK increased
	Common	Musculoskeletal chest pain Pain in extremity Musculoskeletal stiffness	
	Uncommon		Pain in extremity Musculoskeletal chest pain Myalgia[p]
Renal and urinary disorders	Very common	Blood creatinine increased	
General disorders and administration site conditions	Very common	Fatigue[q] Oedema[r] Pyrexia	
	Common	Non cardiac chest pain Chest discomfort Pain	Fatigue[q]
	Uncommon		Pyrexia Oedema[r] Non cardiac chest pain
Investigations	Common	Blood cholesterol increased[s] Weight decreased	
	Uncommon		Weight decreased

ADRs included as preferred terms are based on MedDRA version 22.0.

[a] Includes atypical pneumonia, pneumonia, pneumonia aspiration, pneumonia cryptococcal, lower respiratory tract infection, lower respiratory tract infection viral, lung infection

[b] Includes Grade 5 events

[c] Grade not applicable

[d] Includes headache, sinus headache, head discomfort, migraine, tension headache

[e] Includes paraesthesia, peripheral sensory neuropathy, dysesthesia, hyperesthesia, hypoesthesia, neuralgia, neuropathy peripheral, neurotoxicity, peripheral motor neuropathy, polyneuropathy, burning sensation, post herpetic neuralgia.

[f] Includes altered visual depth perception, cataract, colour blindness acquired, diplopia, glaucoma, intraocular pressure increased, macular oedema, photophobia, photopsia, retinal oedema, vision blurred, visual acuity reduced, visual field defect, visual impairment, vitreous detachment, vitreous floaters, amaurosis fugax

[g] Includes bradycardia, sinus bradycardia

[h] Includes sinus tachycardia, tachycardia, atrial tachycardia, heart rate increased

[i] Includes blood pressure increased, diastolic hypertension, hypertension, systolic hypertension

[j] Includes dyspnoea, dyspnoea exertional

[k] Includes interstitial lung disease, pneumonitis

System organ class	Frequency category	Adverse reactions† all grades	Adverse reactions grade 3-4
[l] Includes abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper, epigastric discomfort [m] Includes aphthous stomatitis, stomatitis, aphthous ulcer, mouth ulceration, oral mucosal blistering [n] Includes dermatitis acneiform, erythema, exfoliative rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, dermatitis, dermatitis allergic, dermatitis contact, generalised erythema, rash follicular, urticaria, drug eruption, toxic skin eruption [o] Includes pruritus, pruritus allergic, pruritus generalised, pruritus genital, vulvovaginal pruritus[p] Includes musculoskeletal pain, myalgia, muscle spasms, muscle tightness, muscle twitching, musculoskeletal discomfort [q] Includes asthenia, fatigue [r] Includes eyelid oedema, face oedema, oedema peripheral, periorbital oedema, swelling face, generalised oedema, peripheral swelling, angioedema, lip swelling, periorbital swelling, skin swelling, swelling of eyelid [s] Includes blood cholesterol increased, hypercholesterolemia †The frequencies for ADR terms associated with chemistry and haematology laboratory changes were determined based on the frequency of abnormal laboratory shifts from baseline.			

DESCRIPTION OF SELECTED ADVERSE REACTIONS

PULMONARY ADVERSE REACTIONS

In ALTA 1L, 2.9% of patients experienced any Grade ILD/pneumonitis early in treatment (within 8 days), with Grade 3-4 ILD/pneumonitis in 2.2% of patients. There were no fatal ILD/pneumonitis. Additionally, 3.7% of patients experienced pneumonitis later in treatment.

In ALTA, pulmonary adverse reactions of any grade, including ILD/pneumonitis, pneumonia and dyspnoea, early in treatment (within 9 days, median onset: 2 days) were experienced in 6.4% of patients; 2.7% of patients had Grade 3-4 pulmonary adverse reactions and 1 patient (0.5%) had fatal pneumonia. Following Grade 1-2 pulmonary adverse reactions, treatment with brigatinib was either interrupted and then restarted or the dose was reduced. Early pulmonary adverse reactions also occurred in a dose escalation study in patients (N = 137) (Study 101) including three fatal cases (hypoxia, acute respiratory distress syndrome and pneumonia) Additionally, 2.3% of patients experienced pneumonitis later in treatment, with 2 patients having Grade 3 pneumonitis (see section 4.2 Dose and Method of Administration and section 4.4 Special Warnings and Precautions for Use).

HYPERTENSION

Hypertension was reported in 30% of patients treated with brigatinib at the 180 mg regimen with 11% having Grade 3 hypertension. Dose reduction for hypertension occurred in 1.5% of patients at the 180 mg regimen. Systolic and diastolic blood pressure increased over time (see section 4.2 Dose and Method of Administration and section 4.4 Special Warnings and Precautions for Use).

BRADYCARDIA

Bradycardia was reported in 8.4% of patients treated with brigatinib at the 180 mg regimen. Heart rates of less than 50 beats per minute (bpm) were reported in 8.4% of patients at the 180 mg regimen (see section 4.2 Dose and Method of Administration and section 4.4 Special Warnings and Precautions for Use).

PERIPHERAL NEUROPATHY

Peripheral neuropathy adverse reactions were reported in 20% of patients treated at the 180 mg regimen with 1.8% having Grade 2 peripheral neuropathy. Thirty-three percent of patients had resolution of all peripheral neuropathy adverse reactions. The median time to onset of peripheral neuropathy was 3.5 months. The median duration of peripheral neuropathy adverse reactions was 6.6 months, with a maximum duration of 28.9 months.

VISUAL DISTURBANCE

Visual disturbance adverse reactions were reported in 14% of patients treated with brigatinib at the 180 mg regimen. Of these, two grade 3 adverse reactions (1.1%) including macular oedema (1) and cataract (2) were reported. Dose reduction for visual disturbance occurred in two patients (0.7%) at the 180 mg regimen (see section 4.2 Dose and Method of Administration and section 4.4 Special Warnings and Precautions for Use).

CREATINE PHOSPHOKINASE (CPK) ELEVATION

In ALTA 1L and ALTA, elevations of creatine phosphokinase (CPK) were reported in 64% of patients treated with brigatinib at the 180 mg regimen. The incidence of Grade 3-4 elevations of CPK was 18%. The median time to onset for CPK elevations was 28 days. Dose reduction for CPK elevation occurred in 6.4% of patients at the 180 mg regimen (see section 4.2 Dose and Method of Administration and section 4.4 Special Warnings and Precautions for Use).

ELEVATIONS OF PANCREATIC ENZYMES

Elevations of amylase and lipase were reported in 47% and 54% of patients treated with brigatinib, respectively at the 180 mg regimen. For elevations to Grades 3 - 4, the incidences for amylase and lipase were 7.7% and 15%, respectively. The median time to onset for amylase elevations and lipase elevations was 16 days and 29 days, respectively. Dose reduction for elevation of lipase and amylase occurred in 4.7% and 2.9% of patients, respectively at the 180 mg regimen (see section 4.2 Dose and Method of Administration and section 4.4 Special Warnings and Precautions for Use).

ELEVATIONS OF HEPATIC ENZYMES

Elevations of ALT and AST were reported in 49% and 68% of patients treated with ALUNBRIG, respectively at the 180 mg regimen. For elevations to Grade 3 and 4, the incidences for ALT and AST were 4.7% and 3.6%, respectively. The median time to onset for ALT elevations and AST elevations was 42 days and 28 days, respectively. Dose reduction for elevation of ALT and AST occurred in 0.7% and 1.1% of patients, respectively at the 180 mg regimen (see sections 4.2 Dose and Method of Administration and 4.4 Special Warnings and Precautions for Use.

HYPERGLYCAEMIA

Sixty one percent of patients experienced hyperglycaemia. Grade 3 hyperglycaemia occurred in 6.6% of patients (see section 4.2 Dose and Method of Administration and section 4.4 Special Warnings and Precautions for Use). No patients had dose reductions due to hyperglycaemia.

PHOTOSENSITIVITY

Photosensitivity was reported in 3.6% patients treated with brigatinib at the 180 mg regimen. Grade 3-4 photosensitivity occurred in 1.1% of patients.

Dose reduction for photosensitivity occurred in two patients (0.7%) at the 180 mg regimen (see sections 4.2 Dose and Method of Administration – Table 2 Other adverse reactions and 4.4 Special Warnings and Precautions for Use – Photosensitivity).

POST-MARKETING

Not applicable.

REPORTING OF SUSPECTED ADVERSE REACTIONS

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no specific antidote for overdose with ALUNBRIG. In the event of an overdose, monitor the patient for adverse reactions [see section 4.8 Adverse Effects (Undesirable Effects)] and provide appropriate supportive care.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: antineoplastic agent, protein kinase inhibitors

MECHANISM OF ACTION

Brigatinib is a tyrosine kinase inhibitor (ALK) of multiple kinases including ALK, ROS1 and insulin-like growth factor 1 receptor (IGF-1R). Among these, brigatinib is most active against ALK. Brigatinib inhibited autophosphorylation of ALK and ALK-mediated phosphorylation of the downstream signalling protein STAT3 in *in vitro* and *in vivo* assays. Brigatinib inhibited the *in vitro* proliferation of cell lines expressing EML4-ALK and NPM-ALK fusion proteins and demonstrated dose-dependent inhibition of EML4-ALK-positive NSCLC xenograft growth in mice. At concentrations (≤ 500 nM) that are achieved clinically, brigatinib inhibited the *in vitro* viability of cells expressing EML4-ALK and most mutant forms associated with resistance to ALK inhibitors including crizotinib. Brigatinib demonstrated *in vivo* and clinical activity against multiple mutant forms of EML4-ALK, including G1202R and L1196M mutants identified in NSCLC tumours in patients who have progressed on crizotinib. Administration of brigatinib resulted in antitumour activity and prolonged survival in mice with an ALK-driven tumour cell line implanted intracranially.

CARDIAC ELECTROPHYSIOLOGY

The QT interval prolongation potential of brigatinib was assessed in 123 patients following once daily ALUNBRIG doses of 30 mg to 240 mg. Brigatinib did not prolong the QT interval to a clinically relevant extent.

CLINICAL TRIALS

ALTA 1L (STUDY 301)

The safety and efficacy of ALUNBRIG was evaluated in a randomised (1:1), open-label, multicentre trial (ALTA 1L) in 275 adult patients with advanced ALK-positive NSCLC who had not previously received an ALK-targeted therapy. Eligibility criteria permitted enrolment of patients with a documented ALK rearrangement based on a local standard of care testing and an ECOG Performance status of 0-2 Patients were allowed to have up to 1 prior regimen of chemotherapy in the locally advanced or metastatic setting. Neurologically stable patients with treated or untreated central nervous system (CNS) metastases, including leptomeningeal metastases, were eligible. Patients with a history of pulmonary interstitial disease, drug-related pneumonitis, or radiation pneumonitis were excluded.

Patients were randomised in a 1:1 ratio to receive ALUNBRIG 180 mg once daily with a 7-day lead-in at 90 mg once daily (N = 137) or crizotinib 250 mg orally twice daily (N = 138). Randomisation was stratified by brain metastases (present, absent) and prior chemotherapy use for locally advanced or metastatic disease (yes, no).

Patients in the crizotinib arm who experienced disease progression were offered crossover to receive treatment with ALUNBRIG. Among all 121 patients who were randomized to the crizotinib arm and discontinued the study treatment by the time of the final analysis, 99 (82%) patients received subsequent ALK TKIs. Eighty (66%) patients who were randomized to the crizotinib arm received subsequent ALUNBRIG treatment, including 65 (54%) patients who crossed over in the study.

The major outcome measure was progression-free survival (PFS) according to Response Evaluation Criteria in Solid Tumours (RECIST v1.1) as evaluated by a Blinded Independent Review Committee (BIRC). Additional outcome measures as evaluated by the BIRC include confirmed objective response rate (ORR), duration of response (DOR), time to response, disease control rate (DCR), intracranial ORR, intracranial PFS, and intracranial DOR. Investigator-assessed outcomes include PFS and overall survival.

Baseline demographics and disease characteristics in ALTA 1L were median age 59 years old (range 27 to 89; 32% 65 and over), 59% White and 39% Asian, 55% female, 39% ECOG PS 0, and 56% ECOG PS 1, 58% never smokers, 93% Stage IV disease, 96% adenocarcinoma histology, 30% CNS metastases at baseline, 14% prior radiotherapy to the brain, and 27% prior chemotherapy. Sites of extra-thoracic metastases include brain (30% of patients), bone (31% of patients), and liver (20% of patients).

At the primary analysis performed at a median follow-up duration of 11 months (range: 0 - 20) in the ALUNBRIG arm, the ALTA 1L study met its primary endpoint demonstrating a statistically significant improvement in PFS by BIRC. A protocol-specified interim efficacy analysis performed at a median follow-up duration of 24.9 months (range: 0 - 34.1) in the ALUNBRIG arm formed the basis for the results from this study (Table 4 and Figure 1). In addition, results from final analysis performed at median follow-up duration of 40.4 months (range: 0 - 52.4) in the ALUNBRIG arm are presented (Table 4).

Table 4: Efficacy Results in ALTA IL (ITT Population) Interim and Final Analyses

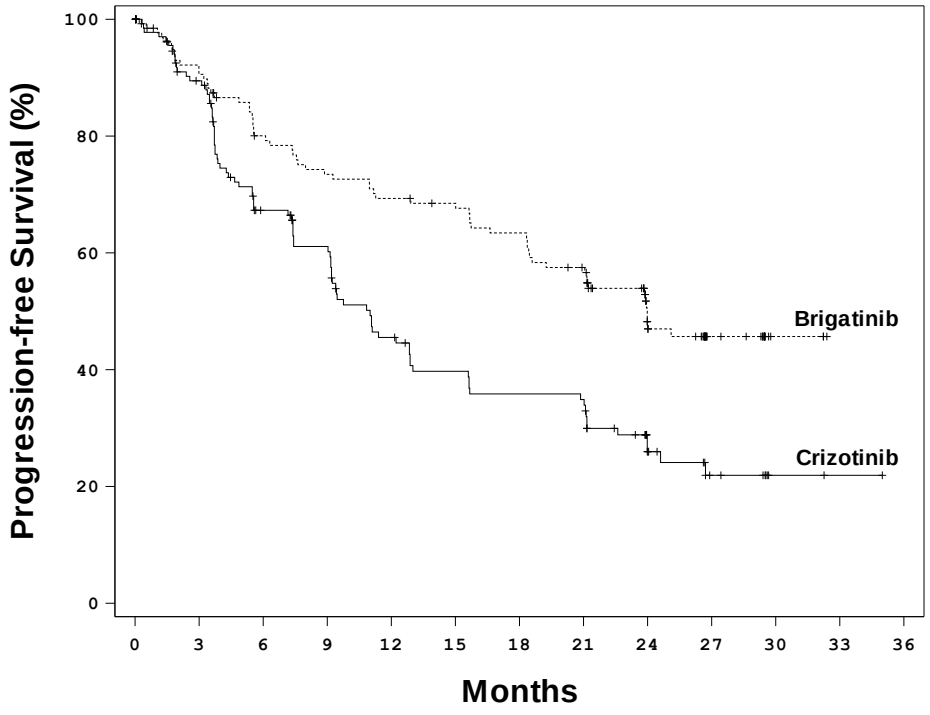
Efficacy Parameters	**ALUNBRIG N = 137**	**CRIZOTINIB N = 138**
Interim Analysis		
Median duration of follow-up (months)	24.9 (range: 0–34.1)	15.2 (range: 0.1–36)
PFS (BIRC)		
Number of Patients with Events, n (%)	63 (46%)	87 (63%)
Progressive Disease, n (%)	56 (40.9%)[a]	82 (59.4%)[b]
Death, n (%)	7 (5.1%)	5 (3.6%)
Median (in months) (95% CI)	24 (18.5, NE)	11 (9.2, 12.9)
Hazard ratio (95% CI)	0.49 (0.35, 0.68)	
Log-rank p-value[c]	<0.0001	
Confirmed Objective Response Rate (BIRC)		
Responders, n (%) (95% CI)	101 (73.7%) (65.5, 80.9)	85 (61.6%) (52.9, 69.7)
p-value[c,d]	0.0342	
Complete Response, %	14.6%	8.7%
Partial Response, %	59.1%	52.9%

Final Analysis		
Median duration of follow-up (months)[e]	40.4 (range 0.0-52.4)	15.2 (range 0.1-51.7)
Duration of Confirmed Response (BIRC)		
Responders, n (%)	102 (74.5%)	86(62.3%)
Median (months) (95% CI)	33.2 (22.1, NE)	13.8 (10.4, 22.1)
Overall Survival[f]		
Number of Events, n (%)	41 (29.9)	51 (37.0)
Median (in months) (95% CI)	NE (NE, NE)	NE (NE, NE)
Hazard ratio (95% CI)	0.806 (0.53, 1.22)	
Log-rank p-value	0.3311	
Overall Survival at 36 months	70.7%	67.5%

BIRC = Blinded Independent Review Committee; NE = Not Estimable; CI = Confidence Interval
[a] includes 2 patients with palliative radiotherapy to the brain
[b] includes 8 patients with palliative radiotherapy to the brain
[c] Stratified by presence of iCNS metastases at baseline and prior chemotherapy for locally advanced or metastatic disease for log-rank test and Cochran Mantel-Haenszel test, respectively
[d] From a Cochran Mantel-Haenszel test
[e]duration of follow up for the whole study
[f] Among all 121 patients who were randomized to the crizotinib arm and discontinued the study treatment by the time of the final analysis, 99 (82%) patients received subsequent ALK TKIs. Eighty (66%) patients who were randomized to the crizotinib arm received subsequent ALUNBRIG treatment, including 65 (54%) patients who crossed over in the study.

The PFS for patients with CNS metastases at baseline (HR = 0.25, 95% CI: 0.14-0.46, median PFS for ALUNBRIG = 24 months, 95% CI: 18.37-NE, median PFS for crizotinib = 5.6 months, 95% CI: 3.84-9.4) and without CNS metastases at baseline (HR = 0.65, 95% CI: 0.44-0.97, median PFS for ALUNBRIG = 24 months, 95% CI: 15.67-NE, median PFS for crizotinib = 13 months, 95% CI: 9.46-21.13), indicated benefit of ALUNBRIG over crizotinib in both subgroups.

Figure 1: Kaplan-Meier Plot of Progression-Free Survival by BIRC in ALTA 1L



Number at Risk												
Brigatinib	137	114	97	89	84	81	75	66	39	18	3	
Crizotinib	138	116	80	68	49	41	37	36	17	8	2	1

At the data cut-off point overall survival data was not mature.

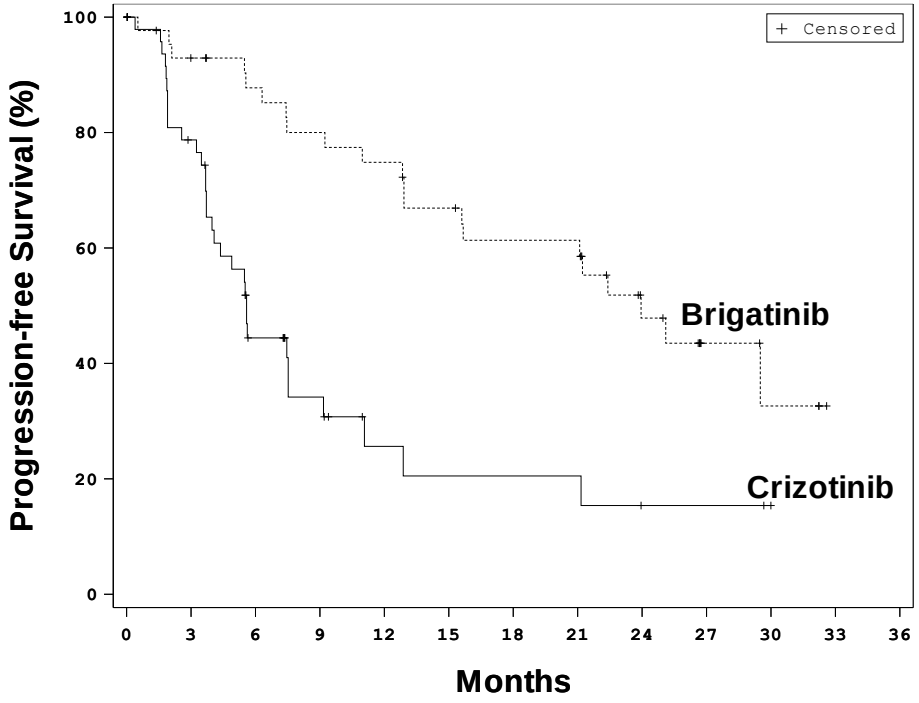
BIRC assessment of intracranial efficacy according to RECIST v1.1 in patients with any brain metastases and patients with measurable brain metastases (≥ 10 mm in longest diameter) at baseline are summarised in Table 5 and Figure 2.

Table 5: BIRC-assessed Intracranial Efficacy in Patients in ALTA 1L

Efficacy Parameters	Patients with Measurable Brain Metastases at Baseline	
	ALUNBRIG N = 18	**Crizotinib N = 23**
Confirmed Intracranial Objective Response Rate		
Responders, n (%) (95% CI)	14 (77.8%) (52.4, 93.6)	6 (26.1%) (10.2, 48.4)
p-value[a,b]	0.0014	
Complete Response %	27.8%	0
Partial Response %	50%	26.1%
Duration of Confirmed Intracranial Response[a,b]		
Responders, n (%)	14 (77.8%)	6 (26.1%)
Median (months) (95% CI)	NE (5.7, NE)	9.2 (3.9, 9.2)
	Patients with Any Brain Metastases at Baseline	
	ALUNBRIG N = 47	**Crizotinib N = 49**
Confirmed Intracranial Objective Response Rate		
Responders, n (%) (95% CI)	31 (66%) (50.7, 79.1)	8 (16.3%) (7.32, 29.7)
p-value[a,b]	< 0.0001	
Complete Response (%)	44.7%	4.1%
Partial Response (%)	21.3%	12.2%
Duration of Confirmed Intracranial Response[c]		
Responders, n (%)	31 (66%)	8 (16.3%)
Median (months) (95% CI)	24 (16.9, NE)	9.2 (3.9, NE)
Intracranial PFS[d]		
Number of Patients with Events, n (%)	21 (44.7%)	32 (65.3%)
Progressive Disease, n (%)	21 (44.7%)[e]	29 (59.2%)[f]
Death, n (%)	0	3 (6.1%)
Median (in months) (95% CI)	24 (13, NE)	5.6 (3.7, 7.5)
Hazard ratio (95% CI)	0.31 (0.17, 0.56)	
Log-rank p-value	< 0.0001	

CI = Confidence Interval; NE = Not Estimable
[a] Stratified by presence prior chemotherapy for locally advanced or metastatic disease for log-rank test and Cochran Mantel-Haenszel test, respectively
[b]From a Cochran Mantel-Haenszel test
[c] measured from date of first confirmed intracranial response until date of intracranial disease progression (new intracranial lesions, intracranial target lesion diameter growth ≥ 20% from nadir, or unequivocal progression of intracranial nontarget lesions) or death or censoring
[d] measured from date of randomisation until date of intracranial disease progression (new intracranial lesions, intracranial target lesion diameter growth ≥20% from nadir, or unequivocal progression of intracranial nontarget lesions) or death or censoring.
[e] includes 1 patient with palliative radiotherapy to the brain
[f] includes 2 patients with palliative radiotherapy to the brain

Figure 2. Kaplan-Meier Plot of Intracranial Progression-Free Survival in Patients with Any Brain Metastases at Baseline by BIRC in ALTA 1L



Number at Risk											
Brigatinib	47	38	34	31	29	25	22	22	12	5	3
Crizotinib	49	36	17	10	5	4	4	4	2	2	

ALTA

The safety and efficacy of ALUNBRIG was evaluated in a randomised (1:1), open-label, multicentre trial (ALTA) in 222 adult patients with locally advanced or metastatic ALK-positive NSCLC who had progressed on crizotinib. Eligibility criteria permitted enrolment of patients with a documented ALK rearrangement based on the Vysis® ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit test either from clinical practice or confirmed by central laboratory, ECOG Performance Status of 0-2, prior chemotherapy, and central nervous system (CNS) metastases provided they were neurologically stable and did not require an increasing dose of corticosteroids. Patients with a history of pulmonary interstitial disease or drug-related pneumonitis were excluded. Patients were randomised in a 1:1 ratio to receive brigatinib either 90 mg once daily (90 mg regimen, n = 112) or 180 mg once daily with 7-day lead-in at 90 mg once daily (180 mg regimen, n = 110). The median duration of follow-up was 17.9 months. Randomisation was stratified by brain metastases (present,

absent) and best prior response to crizotinib therapy (complete or partial response, any other response/unknown). The major outcome measure was confirmed objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumours (RECIST v1.1) as evaluated by investigator. Additional outcome measures included confirmed ORR as evaluated by an Independent Review Committee (IRC); time to response; progression free survival (PFS); duration of response (DOR); overall survival; quality of life; and intracranial ORR, intracranial DOR and intracranial PFS as evaluated by an IRC. The analysis of study measured outcomes across both arms informed the recommended dose.

Baseline demographics and disease characteristics in ALTA were median age 54 years old (range 18 to 82; 23% 65 and over), 67% White and 31% Asian, 57% female, 36% ECOG PS 0 and 57% ECOG PS 1, 95% never or former smokers, 98% Stage IV, 97% adenocarcinoma, and 74% prior chemotherapy. The most common sites of extra-thoracic metastasis included 69% brain (of whom 62% had received prior radiation to the brain), 40% bone, and 26% liver.

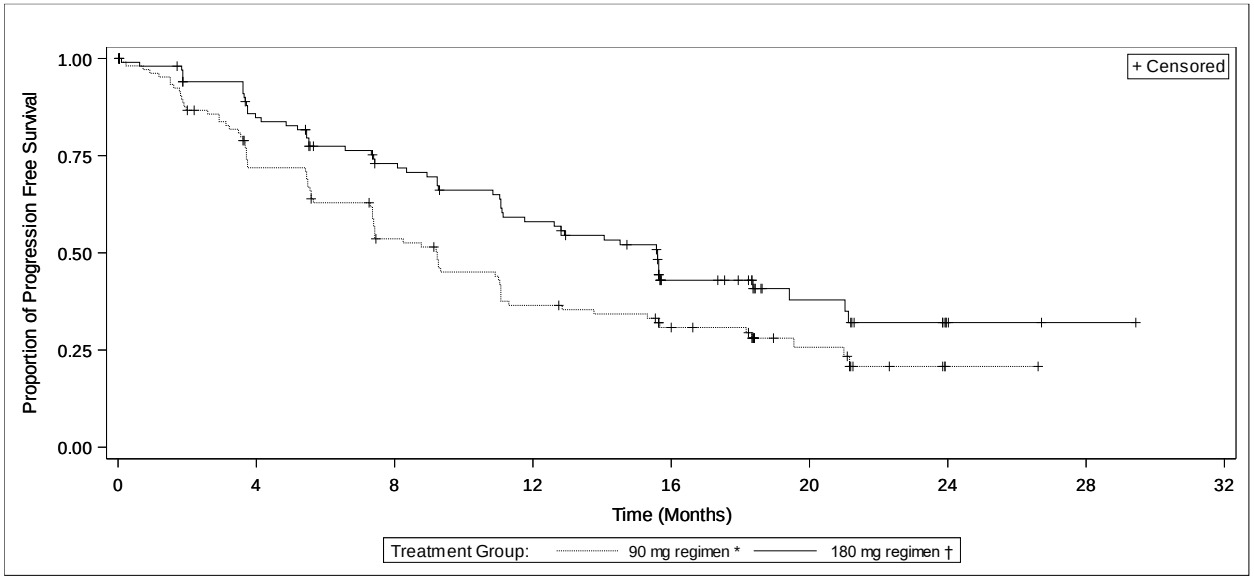
Efficacy results from ALTA analysis are summarised in Table 6 and the Kaplan-Meier (KM) curves for investigator-assessed and IRC-assessed systemic PFS are shown in , **Figure 3** and **Figure 4** respectively.

Table 6: Efficacy Results in ALTA (ITT Population)

Efficacy Parameters	**Investigator Assessment**		**IRC Assessment**	
	90 mg regimen* N = 112	**180 mg regimen† N = 110**	**90 mg regimen* N = 112**	**180 mg regimen† N = 110**
Objective Response Rate				
(%)	45.5%	55.5%	50.9%	54.5%
CI‡	(34.8, 56.5)	(44.3, 66.2)	(41.3, 60.5)	(44.8, 64.1)
Time to response				
Median (months)	1.8	1.9	1.8	1.9
Duration of response				
Median (months)	12.0	13.8	13.8	14.8
95% CI	(9.2, 17.7)	(10.2, 17.5)	(7.4, NE)	(12.6, NE)
Progression-free survival				
Median (months)	9.2	15.6	9.2	16.7
95% CI	(7.4, 11.1)	(11.1, 19.4)	(7.4, 12.8)	(11.6, NE)
Overall survival				
Median (months)	NE	27.6	NA	NA
95% CI	(20.2, NE)	(27.6, NE)	NA	NA
12-month survival probability (%)	70.3%	80.1%	NA	NA

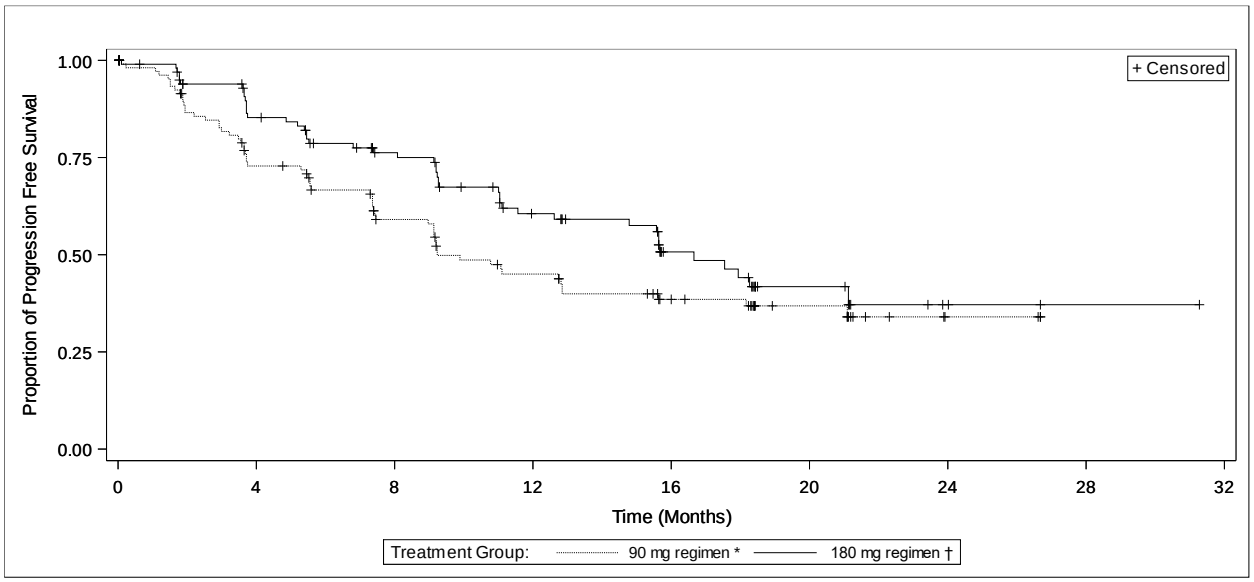
CI = Confidence Interval; NE = Not Estimable; NA = Not Applicable
*90 mg once daily regimen
†180 mg once daily with 7-day lead-in at 90 mg once daily
‡Confidence Interval for investigator assessed ORR is 97.5% and for IRC assessed ORR is 95%

Figure 3: Investigator-Assessed Systemic Progression-Free Survival: ITT Population by Treatment Arm (ALTA)



Abbreviations: ITT = Intent-to-treat
Note: Progression-Free survival was defined as time from initiation of treatment until the date at which disease progression was first evident or death, whichever comes first.
*90 mg once daily regimen
†180 mg once daily with 7-day lead-in at 90 mg once daily

Figure 4: IRC-Assessed Systemic Progression-Free Survival: ITT Population by Treatment Arm (ALTA)



Abbreviations: ITT = Intent-to-treat; IRC = Independent Review Committee
Note: Progression-Free survival was defined as time from initiation of treatment until the date at which disease progression was first evident or death, whichever comes first.
*90 mg once daily regimen
†180 mg once daily with 7-day lead-in at 90 mg once daily

In ALTA, 201 patients had at least 1 evaluable post-baseline assessment out of the 222 patients. Waterfall plots displaying the maximum decrease from baseline in the sum of the longest tumour diameters shows that the majority of patients treated with ALUNBRIG had a reduction in tumour burden in both the 90 mg and 180 mg regimens in ALTA (**Figure 5** and **Figure 6**).

Figure 5: Waterfall Plot of Best Percent Change in Target Lesions from Baseline by Patient Based on Investigator Assessment (ALK-Positive NSCLC) – 90 mg Regimen

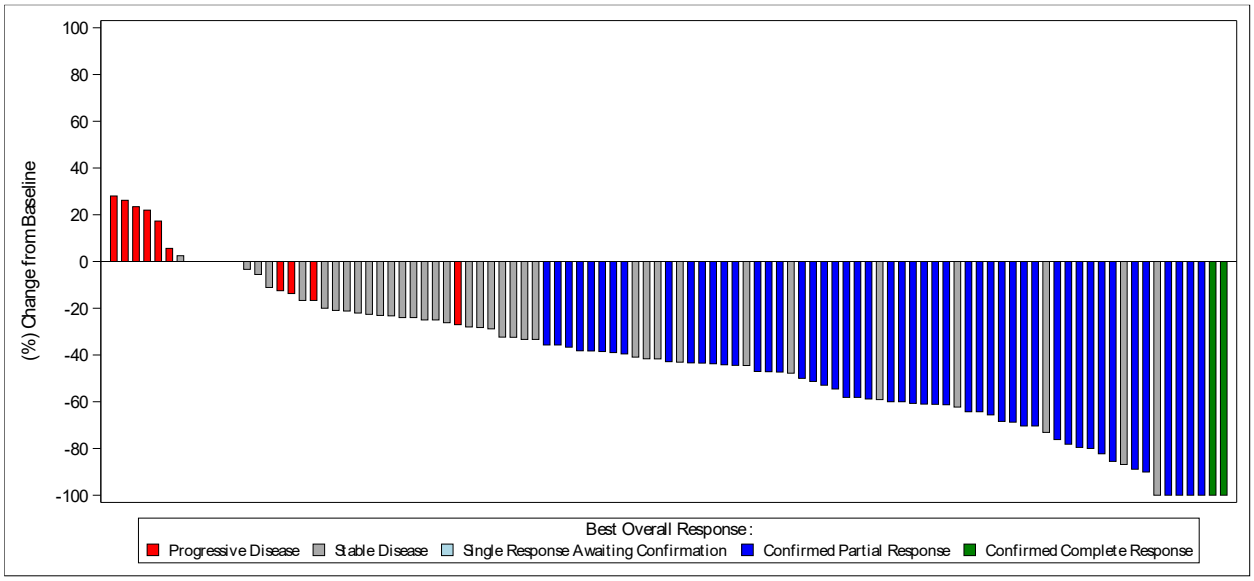
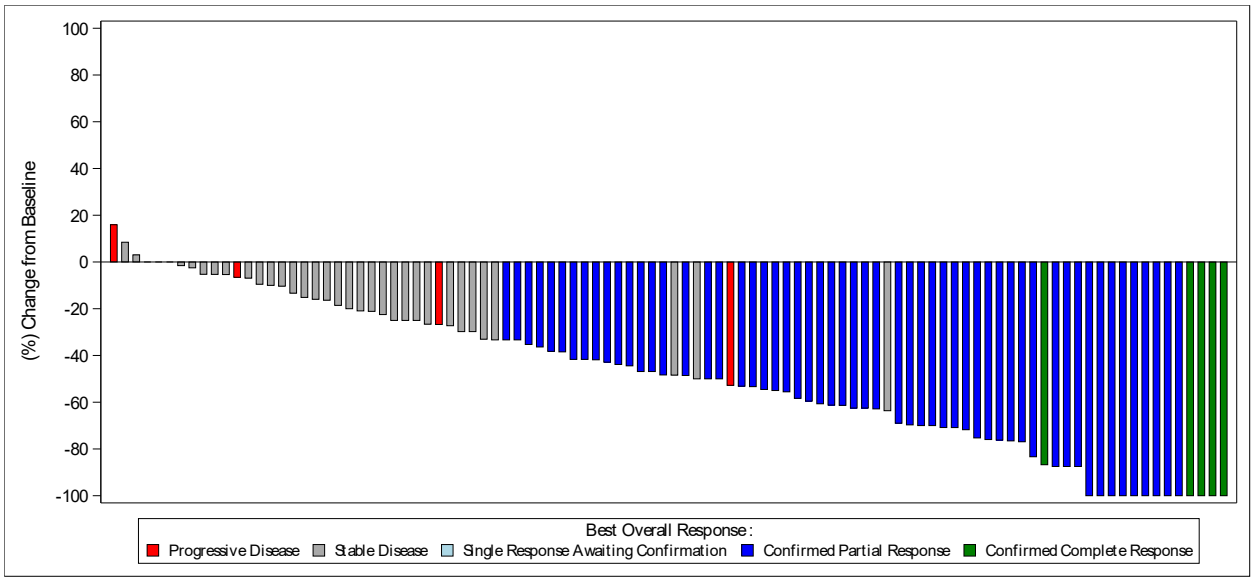


Figure 6: Waterfall Plot of Best Percent Change in Target Lesions from Baseline by Patient Based on Investigator Assessment (ALK-Positive NSCLC) – 180 mg Regimen



Of the 222 enrolled patients, baseline tumour tissue samples were evaluable in 17 patients. Responses were seen in patients with and without secondary ALK kinase domain mutations, including one patient with a secondary ALK kinase domain mutation of G1202R.

IRC assessments of intracranial ORR and duration of intracranial response in patients from ALTA with measurable brain metastases (≥10 mm in longest diameter) at baseline are summarised in **Table 7**.

Table 7: Intracranial Efficacy in Patients with Measurable Brain Metastases at Baseline in ALTA IRC-assessed efficacy parameter

IRC-assessed efficacy parameter	Patients with Measurable Brain Metastases at Baseline	
	90 mg regimen* (N = 26)	**180 mg regimen† (N = 18)**
Intracranial Objective Response Rate		
(%)	50%	67%
95% CI	(30, 70)	(41, 87)
Intracranial Disease Control Rate		
(%)	85%	83%
95% CI	(65, 96)	(59, 96)
Duration of Intracranial Response‡,		
Median (months)	NE	16.6
95% CI	(3.7, NE)	(3.7, 16.6)

CI = Confidence Interval; NE = Not Estimable
*90 mg once daily regimen
†180 mg once daily with 7-day lead-in at 90 mg once daily
‡Events include intracranial disease progression (new lesions, intracranial target lesion diameter growth ≥20% from nadir, or unequivocal progression of intracranial non-target lesions) or death.

In ALTA, patients overall experienced positive changes relative to baseline in quality-of-life (QOL) during treatment with brigatinib. The mean QOL, measured by the summary Global Health Status /QOL score of the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ)-C30, was maintained above baseline mean values throughout follow-up (median: 17.9 months) across both dose groups.

In Study 101, 25 patients with ALK-positive NSCLC that progressed on crizotinib were administered brigatinib at 180 mg once daily with 7-day lead-in at 90 mg once daily regimen. Of these, 19 patients had an investigator-assessed confirmed objective response (76%; 95% CI: 55, 91) the KM median PFS was 16.3 months (95% CI: 9.2, NE) and the 12-month probability of overall survival was 84.0% (95% CI: 62.8, 93.7).

5.2 PHARMACOKINETIC PROPERTIES

ABSORPTION

Following administration of single oral doses of brigatinib of 30 to 240 mg, the median time to peak concentration (T_{max}) ranged from 1 to 4 hours post dose. The geometric mean (CV%) steady-state C_{max} of brigatinib at doses of 90 mg and 180 mg once daily was 552 (65%) and 1452 (60%) ng/mL, respectively, and the corresponding $AUC_{0\text{-}tau}$ was 8165 (57%) and 20276 (56%) h ng/mL, respectively. After a single dose and repeat dosing of brigatinib, systemic exposure was dose proportional over the dose range of 60 mg to 240 mg once daily. The mean accumulation ratio after repeat dosing was 1.9 to 2.4. Brigatinib C_{max} was reduced by 13% with no effect on AUC in healthy subjects administered ALUNBRIG after a high-fat meal compared to the C_{max} and AUC after overnight fasting.

DISTRIBUTION

Brigatinib was 91% bound to human plasma proteins and the binding was not concentration-dependent. The blood-to-plasma concentration ratio is 0.69. Following oral administration of brigatinib 180 mg once daily, the geometric mean apparent volume of distribution (V_z/F) at steady-state was 307 L.

METABOLISM

In vitro studies demonstrated that brigatinib is primarily metabolised by CYP2C8 and CYP3A4. Following oral administration of a single 180 mg dose of [^{14}C]-brigatinib to healthy subjects, N-demethylation and cysteine conjugation were the two major metabolic clearance pathways. Unchanged brigatinib (92%) and its primary metabolite, AP26123 (3.5%), were the major circulating radioactive components. In patients, the steady-state AUC of AP26123 was less than 10% of brigatinib exposure. The metabolite, AP26123, inhibited ALK with approximately 3-fold lower potency than brigatinib *in vitro*.

Excretion

Following oral administration of brigatinib 180 mg once daily, the geometric mean apparent oral clearance (CL/F) of brigatinib at steady-state was 8.9 L/h and the mean plasma elimination half-life was 25 h. Following administration of a single 180 mg oral dose of [^{14}C]-brigatinib to 6 healthy male subjects, 65% of the administered dose was recovered in faeces and 25% of the administered dose was recovered in urine. Unchanged brigatinib represented 41% and 86% of the total radioactivity in faeces and urine, respectively.

Special Populations

RENAL IMPAIRMENT

The pharmacokinetics of brigatinib is similar in patients with normal renal function and in patients with mild or moderate renal impairment (eGFR ≥ 30 mL/min/1.73 m^2) based on the results of population pharmacokinetic analyses. In a pharmacokinetic study, unbound $AUC_{0\text{-}INF}$ was 92% higher in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2, N = 8) as compared to patients with normal renal function (eGFR ≥ 90 mL/min/1.73 m^2, N = 8) (see section 4.2 Dose and Method of Administration).

HEPATIC IMPAIRMENT

The pharmacokinetics of brigatinib was characterised in patients with normal hepatic function (N = 9), mild hepatic impairment (Child-Pugh class A, N = 6), moderate hepatic impairment (Child-Pugh class B, N = 6), or severe hepatic impairment (Child-Pugh class C, N = 6). The pharmacokinetics of brigatinib were similar between patients with normal hepatic function and patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. Unbound $AUC_{0\text{-}INF}$ was 37% higher in patients with severe hepatic impairment (Child-Pugh class C) as compared to patients with normal hepatic function (see section 4.2 Dose and Method of Administration).

AGE, GENDER, RACE

Population pharmacokinetic analyses showed that age, gender or race had no clinically meaningful effect on the pharmacokinetics of brigatinib.

5.3 PRECLINICAL SAFETY DATA

GENOTOXICITY

Brigatinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) or the mammalian cell chromosomal aberration assays, but slightly increased the number of micronuclei in a rat bone marrow micronucleus test and induced polyploidy, endoreduplication and centromeric disruption in human lymphocytes *in vitro*. The mechanism of micronucleus induction was probably abnormal chromosome segregation (aneugenicity) and not a clastogenic effect on chromosomes. Brigatinib potentially induces numerical chromosomal aberrations *in vivo.*

CARCINOGENICITY

Carcinogenicity studies have not been performed with brigatinib.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose monohydrate, microcrystalline cellulose, sodium starch glycollate type A, hydrophobic colloidal silica anhydrous, magnesium stearate, OPADRY II White (PI 11376).

6.2 INCOMPATIBILITIES

Not Applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

ALUNBRIG 30 mg film-coated tablets

PCTFE (Aclar)/Aluminium blister in a pack size of 28 film-coated tablets.

High density polyethylene (HDPE) bottles with a polypropylene (PP) child resistant closure, containing 30 film-coated tablets, and includes a desiccant canister.

ALUNBRIG 90 mg film-coated tablets

PCTFE (Aclar)/Aluminium blister in a pack size of 28 film-coated tablets.

High density polyethylene (HDPE) bottles with a polypropylene (PP) child resistant closure, containing 7 or 30 film-coated tablets, and includes a desiccant canister.

ALUNBRIG 180 mg film-coated tablets

PCTFE (Aclar)/Aluminium blister in a pack size of 28 film-coated tablets.

High density polyethylene (HDPE) bottles with a polypropylene (PP) child resistant closure, containing 30 film-coated tablets, and includes a desiccant canister.

One-month initiation pack

PCTFE (Aclar)/Aluminium foil blister strips containing 7 of the 90 mg film-coated tablets (1 blister of 7 tablets in a carton box) and 21 of the 180 mg film-coated tablets (3 blisters of 7 tablets in a carton box), co-packaged in a single outer carton box.

Not all presentations may be marketed.

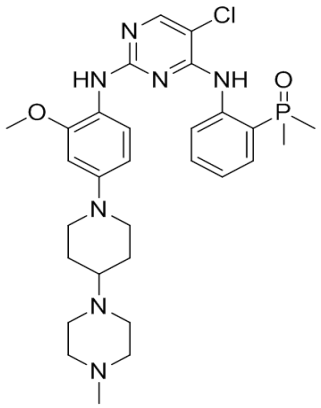
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

CHEMICAL STRUCTURE

The chemical name for brigatinib is 5-chloro-N^4-[2-(dimethylphosphoryl)phenyl]-N^2-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-2,4-diamine. The molecular formula is $C_{29}H_{39}ClN_7O_2P$ which corresponds to a formula weight of 584.1 g/mol. Brigatinib has no chiral centres. The chemical structure is shown below:



Brigatinib is an off-white to beige/tan solid. It is very slightly soluble in water, highly soluble from pH 1.5 – 6.5, slightly soluble in ethanol and soluble in methanol. The pKas were determined to be: 1.73 ± 0.02 (base), 3.65 ± 0.01 (base), 4.72 ± 0.01 (base), and 8.04 ± 0.01 (base).

CAS number

1197953-54-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

6 March 2019

10 DATE OF REVISION

03 June 2022

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Photosensitivity
4.8	Photosensitivity

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