ALUNBRIG

1. NAME OF THE MEDICINAL PRODUCT

Alunbrig 30 mg film-coated tablets
Alunbrig 90 mg film-coated tablets
Alunbrig 180 mg film-coated tablets

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 effec*t
Each film-coated tablet contains 336 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Alunbrig 30 mg film-coated tablets
Round, white to off-white film-coated tablet of approximately 7 mm in diameter with debossed “U3” on one side and plain on the other side.

Alunbrig 90 mg film-coated tablets
Oval, white to off-white film-coated tablet of approximately 15 mm in length with debossed “U7” on one side and plain on the other side.

Alunbrig 180 mg film-coated tablets
Oval, white to off-white film-coated tablet of approximately 19 mm in length with debossed “U13” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Alunbrig is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor.

Alunbrig is indicated as monotherapy for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib

4.2 Posology and method of administration

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

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 (see section 5.1). Assessment for ALK-positive NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilised.

Posology

The recommended starting dose of Alunbrig is 90 mg once daily for the first 7 days, then 180 mg once daily.

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.

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

Treatment should continue as long as clinical benefit is observed.

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

Alunbrig should be permanently discontinued if patient is unable to tolerate the 60 mg once daily 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 event occurs during the first 7 days of treatment, Alunbrig should be withheld until recovery to baseline, then resumed at same dose level and not escalated to 180 mg once daily. • If ILD/pneumonitis occurs after the first 7 days of treatment, Alunbrig should be withheld until recovery to baseline, then resumed at same dose level. • If ILD/pneumonitis recurs, Alunbrig should be permanently discontinued.
	Grade 2	• If ILD/pneumonitis occurs during the first 7 days of treatment, Alunbrig should be withheld until recovery to baseline, then resumed at next lower dose level as described in Table 1 and not escalated to 180 mg once daily. • If ILD/pneumonitis occurs after the first 7 days of treatment, Alunbrig should be withheld until recovery to baseline. Alunbrig should be resumed at next lower dose level as described in Table 1. • If ILD/pneumonitis recurs, Alunbrig should be permanently discontinued.
	Grade 3 or 4	• Alunbrig should be permanently discontinued.
Hypertension	Grade 3 hypertension (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)	• Alunbrig should be withheld until hypertension has recovered to Grade ≤ 1 (SBP < 140 mmHg and DBP < 90 mmHg), then resumed at 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 same dose upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above.

Adverse reaction	Severity*	Dose modification
		• If no concomitant medicinal product known to cause bradycardia is identified, or if contributing concomitant medications are 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 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.
Elevation of 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.
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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 or 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.
Hepatotoxicity	Grade ≥ 3 elevation (> 5.0 × ULN) of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with bilirubin ข 2 × ULN	• Alunbrig should be withheld until recovery to baseline or less than or equal to 3 × ULN, then resumed at next lower dose per Table 1.
	Grade ≥ 2 elevation (> 3 × ULN) of ALT or AST with concurrent total bilirubin	• Alunbrig should be permanently discontinued.

Adverse reaction	Severity*	Dose modification
	elevation > 2 × ULN in the absence of cholestasis or haemolysis	
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.
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 next 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 populations

Elderly patients
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 (see section 4.8). There are no available data on patients over 85 years of age.

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). A reduced starting dose of 60 mg once daily for the first 7 days, then 120 mg once daily is recommended for patients with severe hepatic impairment (Child-Pugh class C) (see section 5.2).

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). A reduced starting dose of 60 mg once daily for the first 7 days, then 90 mg once daily is recommended for patients with severe renal impairment (eGFR < 30 mL/min) (see section 5.2). Patients with severe renal impairment should be closely

monitored for new or worsening respiratory symptoms that may indicate ILD/pneumonitis (e.g., dyspnoea, cough, etc.) particularly in the first week (see section 4.4).

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

Method of administration

Alunbrig is for oral use. The tablets should be swallowed whole and with water. Alunbrig may be taken with or without food.

Grapefruit or grapefruit juice may increase plasma concentrations of brigatinib and should be avoided (see section 4.5).

4.3 Contraindications

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

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).

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 trials.

Some patients experienced pneumonitis later in treatment with Alunbrig.

Patients should be monitored for 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, the dose of Alunbrig should be withheld, and the patient evaluated for other causes of symptoms (e.g., pulmonary embolism, tumour progression, and infectious pneumonia). The dose should be modified accordingly (see section 4.2).

Hypertension
Hypertension has occurred in patients treated with Alunbrig (see section 4.8).

Blood pressure should be monitored regularly during treatment with Alunbrig. Hypertension should be treated according to standard guidelines to control blood pressure. Heart rate should be monitored more frequently in patients if concomitant use of a medicinal product known to cause bradycardia cannot be avoided. 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).

Bradycardia
Bradycardia has occurred in patients treated with Alunbrig (see section 4.8). Caution should be exercised when administering Alunbrig in combination with other agents known to cause bradycardia. Heart rate and blood pressure should be monitored regularly.

If symptomatic bradycardia occurs, treatment with Alunbrig should be withheld and concomitant medicinal products known to cause bradycardia should be evaluated. Upon recovery, the dose should be modified accordingly (see section 4.2). 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).

Visual disturbance
Visual disturbance adverse reactions have occurred in patients treated with Alunbrig (see section 4.8). 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 (see section 4.2).

Creatine phosphokinase (CPK) elevation
Elevations of CPK have occurred in patients treated with Alunbrig (see section 4.8). 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).

Elevations of pancreatic enzymes
Elevations of amylase and lipase have occurred in patients treated with Alunbrig (see section 4.8). 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).

Hepatotoxicity
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).

Hyperglycaemia
Elevations of serum glucose have occurred in patients treated with Alunbrig. Fasting serum glucose should be assessed prior to initiation of Alunbrig and monitored periodically thereafter. Antihyperglycaemic treatment 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 as described in Table 1 may be considered or Alunbrig may be permanently discontinued.

Drug-drug interactions
The concomitant use of Alunbrig with strong CYP3A inhibitors should be avoided. If concomitant use of strong CYP3A inhibitors cannot be avoided, the dose of Alunbrig should be reduced 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.

The concomitant use of Alunbrig with strong and moderate CYP3A inducers should be avoided (see section 4.5). If concomitant use of moderate CYP3A inducers cannot be avoided, the dose of Alunbrig may be increased in 30 mg increments after 7 days pf treatment with the current Alunbrig dose as tolerated, up to a maximum of twice the Alunbrig dose that was tolerated prior to the initiation of the moderate CYP3A inducer. After discontinuation of a moderate CYP3A inducer, Alunbrig should be resumed at the dose that was tolerated prior to the initiation of the moderate CYP3A inducer.

Photosensitivity and photodermatosis

Photosensitivity to sunlight has occurred in patients treated with Alunbrig (see section 4.8). Patients should be advised to avoid prolonged sun exposure while taking Alunbrig, 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), Alunbrig should be withheld until recovery to baseline. The dose should be modified accordingly (see section 4.2).

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).

Lactose

Alunbrig contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially
'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Agents that may increase brigatinib plasma concentrations

CYP3A inhibitors

In vitro studies demonstrated that brigatinib is a substrate of CYP3A4/5. In healthy subjects, 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-INF} by 101% (2-fold), and AUC_{0-120} by 82% (< 2-fold), relative to a 90 mg brigatinib dose administered alone. 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.

Moderate CYP3A inhibitors (e.g., diltiazem and verapamil) may increase the AUC of brigatinib by approximately 40% based on simulations from a physiologically-based pharmacokinetic model. No dose adjustment is required for Alunbrig in combination with moderate CYP3A inhibitors. Patients should be closely monitored when Alunbrig is coadministered with moderate CYP3A inhibitors.

Grapefruit or grapefruit juice may also increase plasma concentrations of brigatinib and should be avoided (see section 4.2).

CYP2C8 inhibitors

In vitro studies demonstrated that brigatinib is a substrate of CYP2C8. In healthy subjects, coadministration of multiple 600 mg twice daily doses of gemfibrozil, a strong CYP2C8 inhibitor, with a single 90 mg brigatinib dose reduced brigatinib C_{max} by 41%, AUC_{0-INF} by 12%, and AUC_{0-120} 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. No dose adjustment is required during coadministration with strong CYP2C8 inhibitors.

P-gp and BCRP inhibitors

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

Agents that may decrease brigatinib plasma concentrations

CYP3A inducers

In healthy subjects, 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-INF} by 80% (5-fold), and AUC_{0-120} by 80% (5-fold), relative to a 180 mg brigatinib dose administered alone. 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.

Moderate CYP3A inducers may decrease the AUC of brigatinib by approximately 50% based on simulations from a physiologically-based pharmacokinetic model. The concomitant use of moderate CYP3A inducers with Alunbrig, including but not limited to efavirenz, modafinil, bosentan, etravirine, and nafcillin should be avoided. If concomitant use of moderate CYP3A inducers cannot be avoided, the dose of Alunbrig may be increased in 30 mg increments after 7 days of treatment with the current Alunbrig dose as tolerated, up to a maximum of twice the Alunbrig dose that was tolerated prior to the initiation of the moderate CYP3A inducer. After discontinuation of a moderate CYP3A inducer, Alunbrig 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

In vitro studies in hepatocytes have shown that brigatinib is an inducer of CYP3A4. In patients with cancer, coadministration of multiple 180 mg daily doses of Alunbrig with a single 3 mg oral dose

of
midazolam, a sensitive CYP3A substrate, decreased midazolam Cmax by 16%, AUC0-INF by 26%, and AUC0-last by 30%, relative to a 3 mg oral dose of midazolam administered alone. Brigatinib may reduce plasma levels of coadministered medicinal products that are predominantly metabolised by CYP3A. Therefore, coadministration of Alunbrig with CYP3A substrates with a narrow therapeutic index (e.g., alfentanil, fentanyl, quinidine, cyclosporine, sirolimus, tacrolimus) should be avoided as their effectiveness may be reduced.

Alunbrig 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).

Transporter substrates
Coadministration of brigatinib with substrates of P-gp, (e.g., digoxin, dabigatran, colchicine, pravastatin), BCRP (e.g., methotrexate, rosuvastatin, sulfasalazine), organic cation transporter 1 (OCT1), multidrug and toxin extrusion protein 1 (MATE1), and 2K (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

Women of childbearing potential/Contraception in males and females

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. Men 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.

Pregnancy

Alunbrig may cause foetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity (see section 5.3). 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 medicinal product, the patient should be apprised of the potential hazard to a foetus.

Breast-feeding

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.

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 (see section 5.3). The clinical relevance of these findings to human fertility is unknown.

4.7 Effects on ability to drive and use machines

Alunbrig has minor influence on the ability to drive and use machines. However, caution should be exercised when driving or operating machines as patients may experience visual disturbance, dizziness, or fatigue while taking Alunbrig.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions (≥ 25%) reported in patients treated with Alunbrig at the recommended dosing regimen were increased AST, increased CPK, hyperglycaemia, increased lipase, hyperinsulinaemia, diarrhoea, increased ALT, increased amylase, anaemia, nausea, fatigue, hypophosphataemia, decreased lymphocyte countcough, increased alkaline phosphatase, rash, increased APTT, myalgia, headache, hypertension, decreased white blood cell count, dysnoea, and vomiting.

The most common serious adverse reactions (≥ 2%) reported in patients treated with Alunbrig at the recommended dosing regimen other than events related to neoplasm progression were pneumonia, pneumonitis, dyspnoea and pyrexia.

Tabulated list of adverse reactions

The data described below reflect exposure to Alunbrig at the recommended dosing regimen in three clinical trials: a Phase 3 trial (ALTA 1L) in patients with advanced ALK-positive NSCLC previously not treated with an ALK-inhibitor (N = 136), a Phase 2 trial (ALTA) in patients treated with Alunbrig with ALK-positive NSCLC who previously progressed on crizotinib (N = 110), and a phase 1/2 dose escalation/expansion trial in patients with advanced malignancies (N = 28). Across these studies, the median duration of exposure in patients receiving Alunbrig at the recommended dosing regimen was 21.8 months.
Adverse reactions reported are presented in Table 3 and are listed by system organ class, preferred term and frequency. Frequency categories are very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, undesirable effects are presented in order of frequency.

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[f] 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	
	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]

System organ class	Frequency category	Adverse reactions† all grades	Adverse reactions Grade 3-4
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[j]
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	Pancreatitis	VomitingStomatitis[m] Dyspepsia Pancreatitis
Hepatobiliary disorders	Very common	AST increased ALT increased Alkaline phosphatase increased	
	Common	Blood lactate dehydrogenase increased Hyperbilirubinaemia	ALT increased AST increased Alkaline phosphatase increased
	Uncommon		Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	Very Common	Rash[n] Pruritus[o]	
	Common	Dry skin Photosensitivity reaction[p]	Rash[n] Photosensitivity reaction[p]
	Uncommon		Dry skin Pruritus[o]
Musculoskeletal and connective tissue disorders	Very common	Blood CPK increased Myalgia[q] Arthralgia	Blood CPK increased
	Common	Musculoskeletal chest pain Pain in extremity Musculoskeletal stiffness	
	Uncommon		Pain in extremity

System organ class	Frequency category	Adverse reactions† all grades	Adverse reactions Grade 3-4
			Musculoskeletal chest pain Myalgia[q]
Renal and urinary disorders	Very common	Blood creatinine increased	
General disorders and administration site conditions	Very common	Fatigue[r] Oedema[s] Pyrexia	
	Common	Non-cardiac chest pain Chest discomfort Pain	Fatigue[r]
	Uncommon		Pyrexia Oedema[s] Non-cardiac chest pain
Investigations	Common	Blood cholesterol increased[t] Weight decreased	
	Uncommon		Weight decreased

† The frequencies for ADR terms associated with chemistry and haematology laboratory changes were determined based on the frequency of abnormal laboratory shifts from baseline.

[a] Includes atypical pneumonia, pneumonia, pneumonia aspiration, pneumoniacryptococcal, 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, dysaesthesia, hyperaesthesia, hypoaesthesia, neuralgia, neuropathy peripheral, neurotoxicity, peripheral motor neuropathy, polyneuropathy, burning sensation, post 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

[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, dermatits contact, generalised erythema, rash follicular, urticaria, drug eruption, toxic skin eruption

[o] Includes pruritus, pruritus allergic, pruritus generalised, pruritus genital, vulvovaginal pruritus

[p] Includes photosensitivity reaction, polymorphic light eruption, solar dermatitis

[q] Includes musculoskeletal pain, myalgia, muscle spasms, muscle tightness, muscle twitching, musculoskeletal discomfort

[r] Includes asthenia, fatigue

[s] 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

[t] Includes blood cholesterol increased, hypercholesterolemia.

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, 6.4% of patients experienced pulmonary adverse reactions of any grade, including ILD/pneumonitis, pneumonia and dyspnoea, early in treatment (within 9 days, median onset: 2 days); 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 Alunbrig 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 in ALTA experienced pneumonitis later in treatment, with 2 patients having Grade 3 pneumonitis (see sections 4.2 and 4.4).

Elderly
Early pulmonary adverse reaction was reported in 10.1% of patients ≥ 65 years of age compared with 3.1% of patients < 65 years of age.

Hypertension
Hypertension was reported in 30% of patients treated with Alunbrig at the 180 mg regimen with 11% having Grade 3 hypertension. Dose reduction for hypertension occurred in 1.5% at the 180 mg regimen. Mean systolic and diastolic blood pressure, in all patients, increased over time (see sections 4.2 and 4.4).

Bradycardia
Bradycardia was reported in 8.4% of patients treated with Alunbrig 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 sections 4.2 and 4.4).

Visual disturbance
Visual disturbance adverse reactions were reported in 14% of patients treated with Alunbrig at the 180 mg regimen. Of these, three Grade 3 adverse reactions (1.1%) including macular oedema and cataract were reported.

Dose reduction for visual disturbance occurred in two patients (0.7%) at the 180 mg regimen (see sections 4.2 and 4.4).

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

Creatine phosphokinase (CPK) elevation
In ALTA 1L and ALTA, elevations of CPK were reported in 64% of patients treated with Alunbrig 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 10% ofpatients at the 180 mg regimen (see sections 4.2 and 4.4).

Elevations of pancreatic enzymes
Elevations of amylase and lipase were reported in 47% and 54% of patients treated with Alunbrig, respectively at the 180 mg regimen. For elevations to Grade 3 and 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 17 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 sections 4.2 and 4.4).

Elevation 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.

Dose reduction for elevation of ALT and AST Occurred in 0.7% and 1.1% of patients, respiectively at the 180 mg regimen (see section 4.2 and 4.4).
Hyperglycaemia
Sixty one percent of patients experienced hyperglycaemia. Grade 3 hyperglycemia occurred in 6.6% of patients.

No patients had dose reductions due to hyperglycaemia.

Photosensitivity and photodermatosis
A pooled analysis from seven clinical trials with data from 804 patients, treated with Alunbrig at different dosing regimens, showed that photosensitivity and photodermatosis was reported in 5.8% of patients and Grade 3-4 occurred in 0.7% of patients. Dose reduction occurred in 0.4% of patients (see sections 4.2 and 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the national reporting system.

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) and provide appropriate supportive care.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agent, protein kinase inhibitors, ATC code: L01ED04

Mechanism of action
Brigatinib is a tyrosine kinase inhibitor that targets ALK, c-ros oncogene 1 (ROS1), and insulin-like growth factor 1 receptor (IGF-1R). 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. Brigatinib inhibited the *in vitro* and *in vivo* viability of cells expressing mutant forms of EML4-ALK associated with resistance to ALK inhibitors, including G1202R and L1196M.

Cardiac electrophysiology
In Study 101, the QT interval prolongation potential of Alunbrig was assessed in 123 patients with

advanced malignancies following once daily brigatinib doses of 30 mg to 240 mg. The maximum mean QTcF *(*corrected QT by the Fridericia method*)* change from baseline was less than 10 msec. An exposure-QT analysis suggested no concentration-dependent QTc interval prolongation Clinical efficacy and safety

ALTA 1L

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 randomised to the crizotinib arm and discontinued study treatment by the time of the final analysis, 99 (82%) patients received subsequent ALK tyrosine kinase inhibitors (TKIs). Eighty (66%) patients who were randomised 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). The median relative dose intensity was 97% for Alunbrig and 99% for crizotinib.

At the primary analysis performed at a median follow-up duration of 11 months 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 analysis with cut-off date of 28 June 2019 was performed at a median follow-up duration of 24.9 months in the Alunbrig arm. The median PFS by BIRC in the ITT population was 24 months in the Alunbrig arm and 11 months in the crizotinib arm (HR =0.49 [95% CI (0.35, 0.68)], p <0.0001).

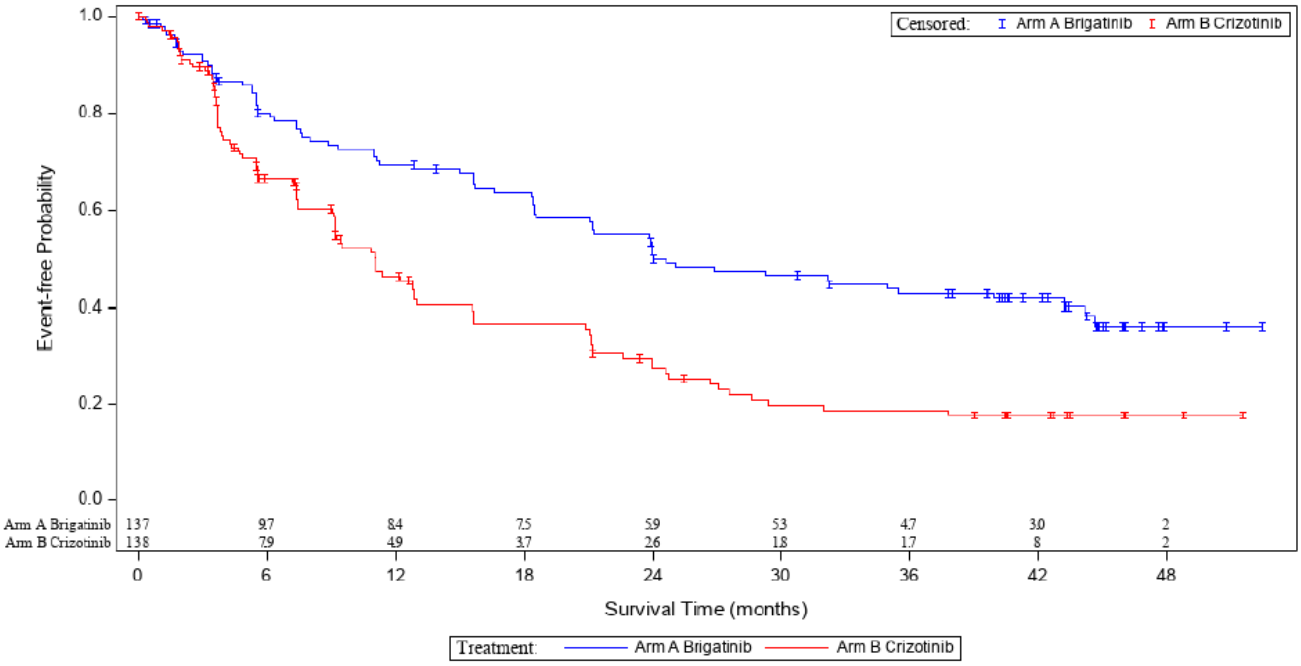
The results from the protocol-specified final analysis with last patient last contact date of 29 January 2021 performed at a median follow-up duration of 40.4 months in the Alunbrig arm are presented below.

Table 4: Efficacy Results in ALTA IL (ITT Population)

Efficacy Parameters	**Alunbrig N = 137**	**Crizotinib N = 138**
Median duration of follow-up (months)[a]	40.4 (range: 0.0–52.4)	15.2 (range: 0.1–51.7)
Primary efficacy parameters		
PFS (BIRC)		
Number of Patients with Events, n (%)	73 (53.3%)	93 (67.4%)
Progressive Disease, n (%)	66 (48.2%)[b]	88 (63.8%)[c]
Death, n (%)	7 (5.1%)	5 (3.6%)
Median (in months) (95% CI)	24 (18.5, 43.2)	11.1 (9.1, 13.0)
Hazard ratio (95% CI)	0.48 (0.35, 0.66)	
Log-rank p-value[d]	<0.0001	
Secondary efficacy parameters		
Confirmed Objective Response Rate (BIRC)		
Responders, n (%) (95% CI)	102 (74.5%) (66.3, 81.5)	86 (62.3%) (53.7, 70.4)
p-value[d,e]	0.0330	
Complete Response, %	24.1%	13.0%
Partial Response, %	50.4%	49.3%
Duration of Confirmed Response (BIRC)		
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)	0.81 (0.53, 1.22)	
Log-rank p-value[d]	0.3311	
Overall Survival at 36 months	70.7%	67.5%

BIRC = Blinded Independent Review Committee; NE = Not Estimable; CI = Confidence Interval
Results in this table are based on final efficacy analysis with last patient last contact date of 29 January 2021.
[a] duration of follow up for the whole study
[b] includes 3 patients with palliative radiotherapy to the brain
[c] includes 9 patients with palliative radiotherapy to the brain
[d] 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
[e] From a Cochran Mantel-Haenszel test
[f] Patient in the crizotinib arm who experienced disease progression were offered crossover to receive treatment with Alunbrig

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



Results in this figure are based on final efficacy analysis with last patient last contact date of 29 January 2021.

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.

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[c]		
Median (months) (95% CI)	27.9 (5.7, NE)	9.2 (3.9, NE)
	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)	7 (14.3%) (5.9, 27.2)
p-value[a,b]	< 0.0001	
Complete Response (%)	44.7%	2.0%
Partial Response (%)	21.3%	12.2%
Duration of Confirmed Intracranial Response[c]		
Median (months) (95% CI)	27.1 (16.9, 42.8)	9.2 (3.9, NE)
Intracranial PFS[d]		
Number of Patients with Events, n (%)	27 (57.4%)	35 (71.4%)
Progressive Disease, n (%)	27 (57.4%)[e]	32 (65.3%)[f]
Death, n (%)	0 (0.0%)	3 (6.1%)
Median (in months) (95% CI)	24.0 (12.9, 30.8)	5.5 (3.7, 7.5)
Hazard ratio (95% CI)	0.29 (0.17, 0.51)	
Log-rank p-value[a]	< 0.0001	

CI = Confidence Interval; NE = Not Estimable
Results in this table are based on final efficacy analysis with last patient last contact date of 29 January 2021.
[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 3 patients with palliative radiotherapy to the brain

ALTA

The safety and efficacy of Alunbrig was evaluated in a randomised (1:1), open-label, multicenter 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 a validated test, ECOG Performance Status of 0-2, and prior chemotherapy. Additionally, patients with central nervous system (CNS) metastases were included, 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 Alunbrig 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 22.9 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; and intracranial ORR and intracranial DOR as evaluated by an IRC.

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, 7% ECOG PS2, 60% never smoker, 35% former smoker, 5% current smoker, 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), 39% bone, and 26% liver.

Efficacy results from ALTA analysis are summarised in Table 6. and the Kaplan-Meier (KM) curve for investigator-assessed PFS is shown in Figure 2.

Table 6: Efficacy results in ALTA (ITT population)

Efficacy parameter	**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				
(%)	46%	56%	51%	56%
CI‡	(35, 57)	(45, 67)	(41, 61)	(47, 66)
Time to response				
Median (months)	1.8	1.9	1.8	1.9
Duration of response				
Median (months)	12.0	13.8	16.4	15.7
95% CI	(9.2,17.7)	(10.2,19.3)	(7.4, 24.9)	(12.8, 21.8)
Progression-free survival				
Median (months)	9.2	15.6	9.2	16.7
95% CI	(7.4, 11.1)	(11.1, 21)	(7.4, 12.8)	(11.6, 21.4)
Overall survival				
Median (months)	29.5	34.1	NA	NA
95% CI	(18.2, NE)	(27.7, NE)	NA	NA
12-month survival probability (%)	70.3%	80.1%	NA	NA

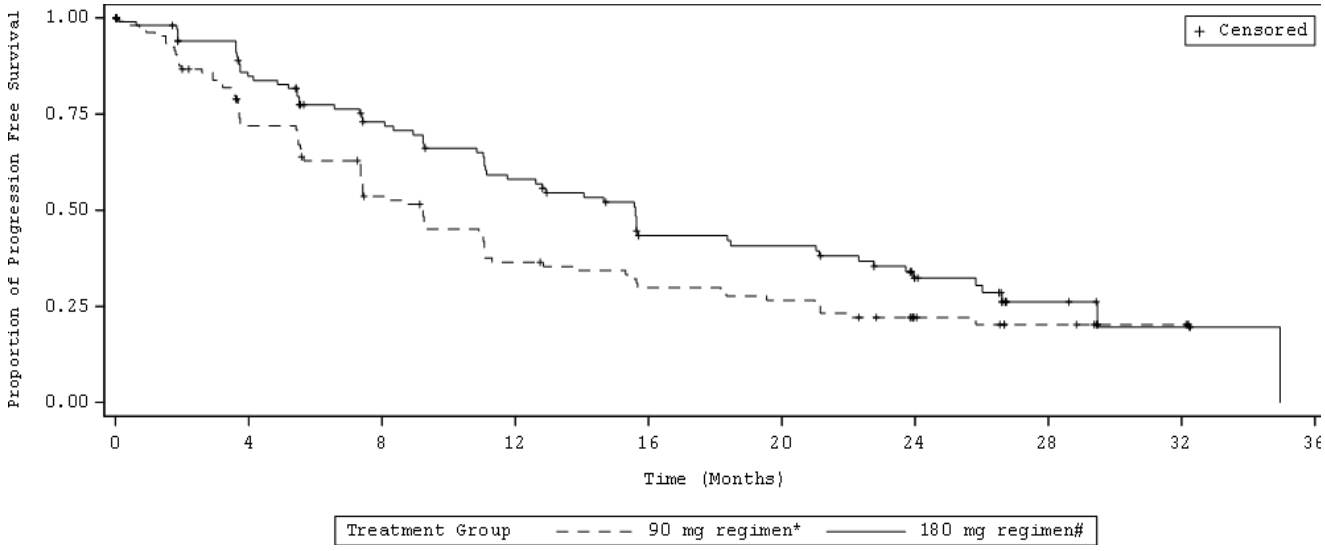
CI = Confidence Interval; NE = Not Estimable; NA = Not Applicable

*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 2*:* 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

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	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)	9.4	16.6
95% CI	(3.7, 24.9)	(3.7, NE)

% 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 patients with any brain metastases at baseline, intracranial disease control rate was 77.8% (95% CI 67.2-86.3) in the 90 mg arm (N = 81) and 85.1% (95% CI 75-92.3) in the 180 mg arm (N=74).

Study 101

In a separate dose finding study, 25 patients with ALK-positive NSCLC that progressed on crizotinib were administered Alunbrig 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) and the KM estimate median duration of response among the 19 responders was 26.1 months (95% CI: 7.9, 26.1). 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).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Alunbrig in all subsets of the paediatric population in lung carcinoma (small cell and non-small cell carcinoma) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

In Study 101, following administration of a single oral dose of brigatinib (30-240 mg) in patients, the median time to peak concentration (T_{max}) was 1-4 hours postdose. After a single dose and at steady state, systemic exposure was dose proportional over the dose range of 60-240 mg once daily. Modest accumulation was observed upon repeated dosing (geometric mean accumulation ratio: 1.9 to 2.4). The geometric mean steady state C_{max} of brigatinib at doses of 90 mg and 180 mg once daily was 552 and 1,452 ng/mL, respectively, and the corresponding $AUC_{0-\tau}$ was 8,165 and 20,276 h·ng/mL, respectively. Brigatinib is a substrate of the transporter proteins P-gp and BCRP.

In healthy subjects, compared to overnight fasting, a high fat meal reduced brigatinib C_{max} by 13% with no effect on AUC. Brigatinib can be administered with or without food.

Distribution

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

Biotransformation

In vitro studies demonstrated that brigatinib is primarily metabolised by CYP2C8 and CYP3A4, and to a much lesser extent by CYP3A5.

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. In urine and faeces combined, 48%, 27%, and 9.1% of the radioactive dose was excreted as unchanged brigatinib, N-desmethyl brigatinib (AP26123), and brigatinib cysteine conjugate, respectively. Unchanged brigatinib was the major circulating radioactive component (92%) along with AP26123 (3.5%), the primary metabolite also observed *in vitro*. In patients, at steady state, the plasma AUC of AP26123 was < 10% of brigatinib exposure. In *in vitro* kinase and cellular assays, the metabolite, AP26123, inhibited ALK with approximately 3-fold lower potency than brigatinib.

Elimination

In patients given 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 median plasma elimination half-life was 24 h.

The primary route of excretion of brigatinib is in faeces. In six healthy male subjects given a single 180 mg oral dose of [^{14}C]brigatinib, 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, the remainder being metabolites.

Specific populations

Hepatic impairment
The pharmacokinetics of brigatinib was characterised in healthy subjects with normal hepatic function (N = 9), and patients with 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 was similar between healthy subjects 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 healthy subjects with normal hepatic function (see section 4.2).

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) based on the results of population pharmacokinetic analyses. In a pharmacokinetic study, unbound $AUC_{0\text{-}INF}$ was 94% higher in patients with severe renal impairment (eGFR < 30 mL/min, N = 6) as compared to patients with normal renal function (eGFR ≥ 90 mL/min, N = 8) (see section 4.2).

Race and gender
Population pharmacokinetic analyses showed that race and gender had no impact on the pharmacokinetics of brigatinib.

Age, body weight, and albumin concentrations
The population pharmacokinetic analyses showed that body weight, age, and albumin concentration had no clinically relevant impact on the pharmacokinetics of brigatinib.

5.3 Preclinical safety data

Safety pharmacology studies with brigatinib identified potential for pulmonary effects (altered respiration rate; 1-2 times the human C_{max}), cardiovascular effects (altered heart rate and blood pressure; at 0.5 times the human C_{max}), and renal effects (reduced renal function; at 1-2.5 times the human C_{max}), but did not indicate any potential for QT prolongation or neurofunctional effects.

Adverse reactions seen in animals at exposure levels similar to clinical exposure levels with possible relevance to clinical use were as follows: gastrointestinal system, bone marrow, eyes, testes, liver, kidney, bone, and heart. These effects were generally reversible during the non-dosing recovery period; however, effects in the eyes and testes were notable exceptions due to lack of recovery.
In repeated dose toxicity studies, lung changes (foamy alveolar macrophages) were noted in monkeys at ≥ 0.2 times the human AUC; however, these were minimal and similar to those reported as background findings in naive monkeys, and there was no clinical evidence of respiratory distress in these monkeys.

Carcinogenicity studies have not been performed with brigatinib.

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. The mechanism of micronucleus induction was abnormal chromosome segregation (aneugenicity) and not a clastogenic effect on chromosomes. This effect was observed at approximately five fold the human exposure at the 180 mg once daily dose.

Brigatinib may impair male fertility. 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 along with microscopic evidence of hypospermatogenesis; these effects were reversible during the recovery period. Overall, these effects on the male reproductive organs in rats and monkeys occurred at exposures ≥ 0.2-times the AUC observed 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.

In an embryo-foetal development study in which pregnant rats were administered daily doses of brigatinib during organogenesis; dose-related skeletal anomalies were observed at doses as low as approximately 0.7-times the human exposure by AUC at the 180 mg once daily dose. Findings included embryo-lethality, reduced foetal growth, and skeletal variations.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycolate (type A)
Silica colloidal hydrophobic
Magnesium stearate

Tablet coating
Talc
Macrogol
Polyvinyl alcohol
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Alunbrig® 30 mg: shelf life 2 years
Alunbrig® 90 mg: shelf life 2 years
Alunbrig® 180 mg: shelf life 2years

6.4 Special precautions for storage

Store in the original container in order to protect from light.

Store below 30ºC

6.5 Nature and contents of container

Alunbrig 30 mg film-coated tablets
Aclar/foil blister strip in carton box, containing either 28, 56 or 112 film-coated tablets.

Alunbrig 90 mg film-coated tablets
Aclar/foil blister strip in carton box, containing either 7 or 28 film-coated tablets.

Alunbrig 180 mg film-coated tablets
Aclar/foil blister strip in carton box, containing 28 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Patients should be advised to keep the desiccant canister in the bottle and not to swallow it.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7. MARKETING AUTHORISATION HOLDER

Imported by: Takeda (Thailand) Ltd., Bangkok, Thailand

8. MARKETING AUTHORISATION NUMBER(S)

Alunbrig® 30 mg: Reg.No. 1C 15125/62 (N)
Alunbrig® 90 mg: Reg.No. 1C 15126/62 (N)
Alunbrig® 180 mg: Reg.No. 1C 15127/62 (N)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

7 November 2019

10. DATE OF REVISION OF THE TEXT

Jul 2023