PRESCRIBING INFORMATION

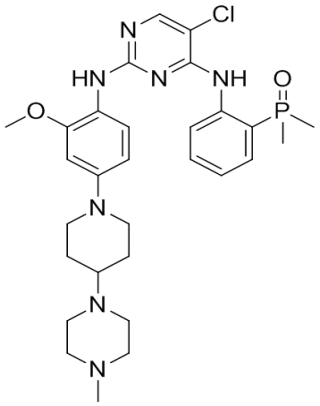
1. NAME OF THE MEDICINAL PRODUCT

ALUNBRIG® (brigatinib)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 30 mg, 90 mg, 180 mg of brigatinib.

Brigatinib is a kinase inhibitor. 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 584.10 g/mol. Brigatinib has no chiral centers. The chemical structure is shown below:



Brigatinib is an off-white to beige/tan solid. The pK_as 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).

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets:

Available Pharmaceutical Forms	Strength	Color	Shape	Markings
Film-coated Tablets	30 mg	White to off-white	Round	debossed "U3" on one side and plain on the other side
	90 mg	White to off-white	Oval	debossed "U7" on one side and plain on the other side
	180 mg	White to off-white	Oval	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 advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor.

ALUNBRIG® is indicated for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib.

4.2 Posology and Method of Administration

ALK Testing

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

Dosage

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	NA*
180 mg once daily	reduce to 120 mg once daily	reduce to 90 mg once daily	reduce to 60 mg once daily

*Not applicable

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 summarized in Table 2.

Table 2: Recommended ALUNBRIG® Dose Modifications for Adverse Reactions

Adverse Reaction	Severity*	Dose Modification
Interstital 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 event 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 event 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 is suspected

Adverse Reaction	Severity*	Dose Modification
		• If event occurs after the first 7 days of treatment, ALUNBRIG® should be withheld until recovery to baseline. If ILD/pneumonitis is suspected, ALUNBRIG® should be resumed at next lower dose level as described in Table 1. Otherwise, ALUNBRIG® can be resumed at the same dose. • If event 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 1or permanently discontinued • If Grade 4 hypertension recurs, ALUNBRIG® should be permanently discontinued.
Bradycardia (HR 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. • If no concomitant medication known to cause bradycardia is identified, or if contributing concomitant medications are not discontinued or

Adverse Reaction	Severity*	Dose Modification
		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.
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 reccurs, 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 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with	• ALUNBRIG® should be withheld until recovery to to baseline or less than or equal to 3 x ULN, then resumed at next lower dose per Table 1.

Adverse Reaction	Severity*	Dose Modification
	bilirubin ≤ 2 × ULN	
	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.
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; HR = heart rate; SBP = systolic blood pressure; ULN = upper limit of normal		

Special Patient 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 ACTION AND CLINICAL PHARMACOLOGY). There are limited data on patients over 85 years of age.

Pediatric Patients

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

Impaired Renal Function

No dose adjustment is recommended for patients with mild or moderate renal impairment (creatinine clearance ≥ 30 mL/min). The dose of Alunbrig should be reduced by approximately 50% (e.g., from 180 mg to 90 mg, or from 90 mg to 60 mg) 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 ACTION AND CLINICAL PHARMACOLOGY).

Impaired Hepatic Function

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 Alunbrig should be reduced by approximately 40% (e.g., 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 ACTION AND CLINICAL PHARMACOLOGY).

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.

4.4 Special Warnings and Special 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®.

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, 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).

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 medications 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 disturbances 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 (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).

Pancreatic Enzyme Elevation

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).

Photosensitivity

Photosensitivity to sunlight has occurred in patients treated with brigatinib (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 $\geq$ 30) to help protect against potential sunburn. For severe photosensitivity reactions ($\geq$ Grade 3), brigatinib should be withheld until recovery to baseline. The dose should be modified accordingly (see section 4.2).

Hyperglycemia

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. Antihyperglycemic medications should be initiated or optimized as needed. If adequate hyperglycemic control cannot be achieved with optimal medical management, ALUNBRIG® should be withheld until adequate hyperglycemic control is achieved; upon recovery reducing the dose of ALUNBRIG® as described

in section 4.2 may be considered or ALUNBRIG® may be permanently discontinued.

Elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST)

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).

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 moderate CYP3A inhibitors (e.g. diltiazem and verapamil) with ALUNBRIG® should be avoided. If concomitant use of moderate CYP3Ainhibitors cannot be avoided, the dose of ALUNBRIG® should be reduced by approximately 40% (e.g., 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, ALUNBRIG® should be resumed at the dose that was tolerated prior to the initiation of the moderate 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 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 CPY3A inducer, ALUNBRIG® should be resumed at the dose that was tolerated prior to the initiation of the moderate CYP3A inducer.

Embryo-Fetal Toxicity

Based on its mechanism of action and findings in animals, ALUNBRIG® can cause fetal harm when administered to pregnant women. There are no clinical data on the use of ALUNBRIG® in pregnant women.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential 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).

4.5 Interaction with Other Medications and Other Forms of Interaction

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., itraconazole, ketoconazole, posaconazole, 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.

The concomitant use of moderate CYP3A inhibitors (e.g. diltiazem and verapamil) with ALUNBRIG® should be avoided. If concomitant use of moderate CYP3Ainhibitors cannot be avoided, the dose of ALUNBRIG® should be reduced by approximately 40% (e.g., 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, ALUNBRIG® 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.

P-gp and BCRP Inhibitors

No dose adjustment is required for ALUNBRIG® during coadministration with P-gp and BCRP inhibitors.

Agents that may decrease brigatinib plasma concentrations

CYP3A Inducers

The concomitant use of strong CYP3A inducers with ALUNBRIG®, including but not limited to rifampin, carbamazepine, phenytoin, rifabutin, phenobarbital, and St. John's Wort should be avoided.

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 CPY3A 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

Brigatinib induces CYP3A in vitro and reduces plasma concentrations of coadministered medications that are predominantly metabolized by CYP3A. 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.

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).

Transporter Substrates

Brigatinib is an inhibitor of P-gp, BCRP, OCT1, MATE1, and 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 Pregnancy and Lactation

Pregnancy

ALUNBRIG® may cause fetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity (see NON-CLINICAL TOXICOLOGY). 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 a 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 patient 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 embryo-fetal development study in which pregnant rats were administered daily doses of brigatinib during organogenesis, dose-related skeletal (incomplete ossification, small incisors) and visceral anomalies were observed at doses as low as 12.5 mg/kg/day (approximately 0.7 times the human exposure by AUC at 180 mg once daily). Malformations observed at 25 mg/kg/day (approximately 1.26 times the human AUC at 180 mg once daily) included anasarca (generalized subcutaneous edema), 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.

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®.

Fertility

No human data on the effect of ALUNBRIG® on fertility are available. Based on reproductive studies in male animals, ALUNBRIG® may cause reduced fertility in males (see NON-CLINICAL TOXICOLOGY). The clinical relevance of these findings to human fertility is unknown.

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 Undesirable Effects

Clinical Trials

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

- Study 301 (ALTA 1L): A randomized, open-label multicenter trial in patients with advanced ALK-positive NSCLC who had not previously received an ALK-targeted therapy. Patients were randomized 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+ 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 multicenter phase 1/2 dose escalation/ expansion trial in patients with advanced malignancies.

The most common adverse reactions reported in patients (≥25%) treated with ALUNBRIG® at the 180 mg regimen were increased AST (68%), increased CPK (64%), hyperglycemia (61%), increased lipase (54%), hyperinsulinemia (53%), diarrhea (49%), increased ALT (49%), increased amylase (47%), anemia (47%), nausea (40%), fatigue (40%), hypophosphatemia (39%), decreased lymphocyte count (39%), cough (38%), rash (37%), increased alkaline phosphatase (37%), increased APTT (36%), myalgia (34%), headache (33%), hypertension (30%), white blood count decreased (28%), dyspnea (27%), and vomiting (26%).

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

Treatment-emergent adverse events 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 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 Organizations 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†,‡‡ Upper respiratory tract infection	
	Common		Pneumonia†
Blood and lymphatic disorders	Very common	Anemia Lymphocyte count decreased APTT increased White blood cell count decreased Neutrophil count decreased	Lymphocyte count decreased
	Common	Decreased platelet count	APTT increased Anemia
	Uncommon		Neutrophil count decreased
Metabolism and nutrition disorders	Very common	Hyperglycemia Hyperinsulinemia‡ Hypophosphatemia Hypomagnesemia Hypercalcemia Hyponatremia	

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
		Hypokalemia Decreased appetite	
	Common		Hypophosphatemia Hyperglycemia Hyponatremia Decreased appetite Hypokalemia
Psychiatric disorders	Common	Insomnia	
Nervous system disorders	Very common	Headache[§] Peripheral neuropathy[¶] Dizziness	
	Common	Dysgeusia Memory Impairment	Headache[§] Peripheral neuropathy[¶]
	Uncommon		Dizziness
Eye disorders	Very common	Visual Disturbance[#]	
	Common		Visual disturbance[#]
Cardiac disorders	Common	Bradycardia[β] Electrocardiogram QT prolonged Tachycardia[Þ] Palpitations	Electrocardiogram QT prolonged
	Uncommon		Bradycardia[β]
Vascular disorders	Very Common	Hypertension[à]	Hypertension[à]
	Common		
Respiratory, thoracid and mediastinal disorders	Very Common	Cough Dyspnea[è]	
	Common	Pneumonitis[ø]	Pneumonitis[ø] Dyspnea[è]
Gastrointestinal disorders	Very common	Lipase increased Diarrhea Amylase increased Nausea Vomiting Abdominal pain[ý] Constipation Stomatitis[£]	Lipase increased
	Common	Dry mouth Dyspepsia Flatulence	Amylase increased Nausea Abdominal pain[ý] Diarrhea
	Uncommon		Vomiting Stomatitis[£] Dyspepsia
	Very common	AST increased	

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
Hepatobiliary disorders		ALT increased Alkaline phosphatase increased	
	Common	Blood lactate dehydrogenase increased Hyperbilirubinaemia	ALT increased AST increased Alkaline phosphatase increased
Skin and subcutaneous tissue disorders	Very Common	Rash[¥] Pruritus[OE]	
	Common	Dry skin Photosensitivity reaction	Rash[¥] Photosensitivity reaction
	Uncommon		Dry skin Pruritus[OE]
Musculoskeletal and connective tissue disorders	Very common	Blood CPK increased Myalgia[oe] Arthralgia	Blood CPK increased
	Common	Musculoskeletal chest pain Pain in extremity Musculoskeletal stiffness	
	Uncommon		Pain in extremity Musculoskeletal chest pain Myalgia[oe]
Renal and urinary disorders	Very common	Blood creatinine increased	
General disorders and administration site conditions	Very common	Fatigue[Ð] Edema[††] Pyrexia	
	Common	Non-cardiac chest pain Chest discomfort Pain	Fatigue[Ð]
	Uncommon		Pyrexia Edema[††] Non-cardiac chest pain
Investigations	Common	Blood cholesterol increased Weight decreased	
	Uncommon		Weight decreased

ADRs included as preferred terms are based on MedDRA version 22.0.
Database Cutoff Date: Study 101 – 31May2016, Study 201 – 29Sep2017, Study 301 – 28Jun2019
APTT increased frequency based on Studies 101 and 201
Increased CPK frequency based on Studies 201 and 301
* The frequencies for ADR terms associated with chemistry and hematology laboratory changes were determined based on the frequency of abnormal laboratory shifts from baseline.
† –Includes atypical pneumonia, pneumonia, pneumonia aspiration, lower respiratory tract infection, lower respiratory tract infection viral, lung infection, pneumonia cryptococcal

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

‡ Grade not applicable
§ Includes headache, sinus headache, head discomfort, migraine, tension headache
¶ Includes paresthesia, peripheral sensory neuropathy, dysesthesia, hyperesthesia, hypoesthesia, neuralgia, neuropathy peripheral, neurotoxicity, peripheral motor neuropathy, polyneuropathy, burning sensation, post herpetic neuralgia
# Includes altered visual depth perception, cataract, color blindness acquired, diplopia, glaucoma, intraocular pressure increased, macular edema, photophobia, photopsia, retinal edema, vision blurred, visual acuity reduced, visual field defect, visual impairment, vitreous detachment, vitreous floaters, amaurosis fugax
β Includes bradycardia, sinus bradycardia
Þ Includes sinus tachycardia, tachycardia, atrial tachycardia, heart rate increased
à Includes blood pressure increased, diastolic hypertension, hypertension, systolic hypertension
è Includes dyspnea, dyspnea exertional
ø Includes interstitial lung disease, pneumonitis
ý Includes abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper, epigastric discomfort
£ Includes aphthous stomatitis, stomatitis, aphthous ulcer, mouth ulceration, oral mucosal blistering
¥ 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, generalized erythema, rash follicular, urticaria, drug eruption, toxic skin eruption
ÖE Includes pruritus, pruritus allergic, pruritus generalised, pruritus genital, vulvovaginal pruritus
øe Includes musculoskeletal pain, myalgia, muscle spasms, muscle tightness, muscle twitching, musculoskeletal discomfort
Ð Includes asthenia, fatigue
†† Includes eyelid edema, face edema, edema peripheral, periorbital edema, swelling face, generalized edema, peripheral swelling, angioedema, lip swelling, periorbital swelling, skin swelling, swelling of eyelid
Includes blood cholesterol increased, hypercholesterolemia
‡‡ Includes fatal events

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 dyspnea, 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. Additionally, 2.3% of patients experienced pneumonitis later in treatment, with 2 patients having Grade 3 pneumonitis (see section 4.2 and section 4.4).

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. (see section 4.2 and section 4.4).

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. In a separate dose finding study (Study 101), a decrease in heart rate was associated with increased brigatinib plasma concentrations (Cmax) (see section 4.2 and section 4.4).

Visual Disturbance

Visual disturbances were reported in 14% of patients treated with brigatinib at the 180 mg regimen. Of these, three 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 and section 4.4).

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 10% patients at the 180 mg regimen (see section 4.2 and section 4.4).

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.

The elevations of amylase and lipase were not associated with clinical pancreatitis in Study 201.

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 and section 4.4).

Elevations of Hepatic Enzymes

Elevations of ALT and AST occurred in 49% and 68% of patients treated with brigatinib, respectively at the 180 mg regimen. For elevations to Grades 3 - 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 section 4.2 and section 4.4).

Hyperglycemia

Sixty-one percent of patients experienced hyperglycemia. Grade 3 hyperglycemia occurred in 6.6% of patients (see section 4.2 and section 4.4).

No patients had dose reductions due to hyperglycaemia.

Photosensitivity

Photosensitivity was reported in 3.6% patients treated with ALUNBRIG® 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 section 4.2 and section 4.4).

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.

4.10 Drug Abuse and Dependence

ALUNBRIG® has no known potential for abuse or dependence.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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.

Mechanism of Action

Brigatinib is a tyrosine kinase inhibitor (TKI) that targets 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 17 mutant forms associated with resistance to ALK inhibitors including crizotinib. No ALK mutations associated with resistance to brigatinib were observed. 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 antitumor activity and prolonged survival in mice with an ALK-driven tumour cell line implanted intracranially.

Clinical Studies

Advanced ALK-Positive NSCLC Without Prior ALK-targeted Therapy (ALTA 1L, Study 301)

The safety and efficacy of brigatinib was evaluated in a randomized (1:1), open-label, multicenter 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 randomized in a 1:1 ratio to receive brigatinib 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). Randomization 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 brigatinib. Among all 121 patients who were randomized to the crizotinib arm and discontinued 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 brigatinib 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 Tumors (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 (Table 4) 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 brigatinib 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 brigatinib arm formed the basis for the results from this study (Table 5 and Figure 1). In addition, results from final analysis performed at median follow-up duration of 40.4 months in the Alunbrig arm are presented (Table 5).

Table 4. Demographics and Disease Characteristics of ALK-positive Patients treated with Brigatinib and Crizotinib in ALTA 1L

Characteristic	Brigatinib (N = 137)	Crizotinib (N = 138)	Total (N = 275)
Sex, n (%)			
Male	68 (49.6)	57 (41.3)	125 (45.5)
Female	69 (50.4)	81 (58.7)	150 (54.5)
Age (years)			
Median (range)	58 (27-86)	60 (29-89)	59 (27-89)
Race, n (%)			
White	76 (55.5)	86 (62.3)	162 (58.9)
Asian	59 (43.1)	49 (35.5)	108 (39.3)
Other	2 (1.5)	3 (2.2)	5 (1.8)
ECOG performance status, n (%)			
0	58 (42.3)	60 (43.5)	118 (42.9)
1	73 (53.3)	72 (52.2)	145 (52.7)
2	6 (4.4)	6 (4.3)	12 (4.4)
Smoking History, n (%)			
No	84 (61.3)	75 (54.3)	159 (57.8)
Yes	53 (38.7)	63 (45.7)	116 (42.2)
Histology, n (%)			
Adenocarcinoma	126 (92.0)	137 (99.3)	263 (95.6)
Squamous	4 (2.9)	0	4 (1.5)
Large cell	2 (1.5)	0	2 (0.7)
Adenosquamous Carcinoma	3 (2.2)	1 (0.7)	4 (1.5)
Other	2 (1.5)	0	2 (0.7)
Brain metastases at baseline*, n (%)			
Present	40 (29.2)	41 (29.7)	81 (29.5)
Patients with prior radiotherapy to the brain, n (%)			
Yes	18 (13.1)	19 (13.8)	37 (13.5)
Prior chemotherapy in locally advanced or metastatic setting, n (%)			
Yes	36 (26.3)	37 (26.8)	73 (26.5)

* As assessed by the investigator

Table 5. Efficacy Results in ALTA IL (ITT Population) Interim and Final Analyses

Efficacy Parameters	**Brigatinib 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	
PFS at 6 months	80.1%	67.3%
PFS at 12 months	69.3%	45.5%
PFS at 18 months	63.4%	35.8%
PFS at 24 months	48.2%	26%
PFS (Investigator)		
Number of Patients with Events, n (%)	59 (43.1%)	92 (66.7%)
Progressive Disease, n (%)	51 (37.2%)	88 (63.8%)
Death, n (%)	8 (5.8%)	4 (2.9%)
Median (in months) (95% CI)	29.4 (21.2, NE)	9.2 (7.4, 12.9)
Hazard ratio (95% CI)	0.43 (0.31, 0.61)	
Log-rank p-value[c]	<0.0001	
PFS at 6 months	80.4%	65.1%
PFS at 12 months	69.4%	43.3%
PFS at 18 months	63%	33.9%
PFS at 24 months	55.6%	23.6%
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)
Response duration at 12 months	77.8%	56.1%
Response duration at 24 months	54.5%	34.8%
Response duration at 36 months	48.9%	24.5%
Response duration at 48 months	39.5%	24.5%

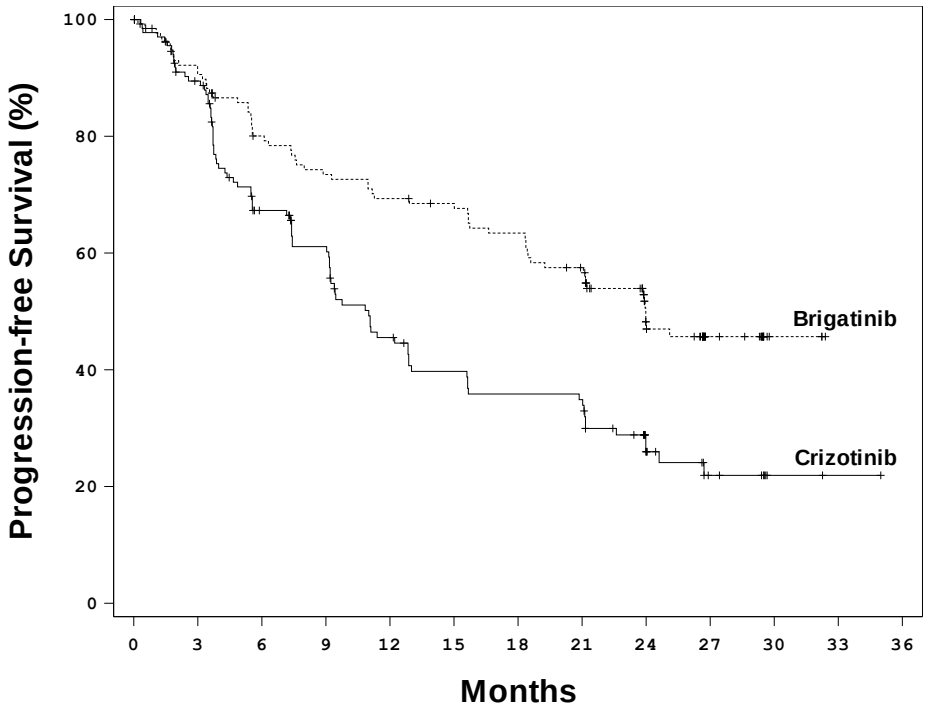
Table 5. Efficacy Results in ALTA IL (ITT Population) Interim and Final Analyses

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[d]	0.3311	
Overall Survival at 12 months	85.3%	86.8%
Overall Survival at 24 months	75.8%	73.8%
Overall Survival at 36 months	70.7%	67.5%
Overall Survival at 48 months	66.1%	60.2%

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 study treatment by the time of the final analysis, ninety-nine (82%) patients received subsequent ALK TKIs. Eighty (66%) patients who were randomized to the crizotinib arm received subsequent brigatinib treatment, including sixty-five (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 brigatinib = 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 brigatinib = 24 months, 95% CI: 15.67-NE, median PFS for crizotinib = 13 months, 95% CI: 9.46-21.13), indicated benefit of brigatinib 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 summarized in Table 6 and Figure 2.

Table 6. BIRC-assessed Intracranial Efficacy in Patients in ALTA 1L

Efficacy Parameters	Patients with Measurable Brain Metastases at Baseline	
	Brigatinib 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]		
Responders, n (%)	14 (77.8%)	6 (26.1%)
Median (months) (95% CI)	NE (5.7, NE)	9.2 (3.9, 9.2)
Intracranial response duration at 6 months	83.3%	60%
Intracranial response duration at 12 months	75%	NE
Intracranial response duration at 18 months	64.3%	NE
Intracranial response duration at 24 months	64.3%	NE
	Patients with Any Brain Metastases at Baseline	
	Brigatinib 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, n (%)	44.7%	4.1%
Partial Response, n (%)	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 response duration at 6 months	93.1%	71.4%
Intracranial response duration at 12 months	79.2%	35.7%
Intracranial response duration at 18 months	67.5%	35.7%
Intracranial response duration at 24 months	55%	NE

Table 6. BIRC-assessed Intracranial Efficacy in Patients in ALTA 1L

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	
Intracranial PFS at 6 months	87.7%	44.4%
Intracranial PFS at 12 months	74.8%	25.6%
Intracranial PFS at 18 months	61.3%	20.5%
Intracranial PFS at 24 months	47.9%	15.4%

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

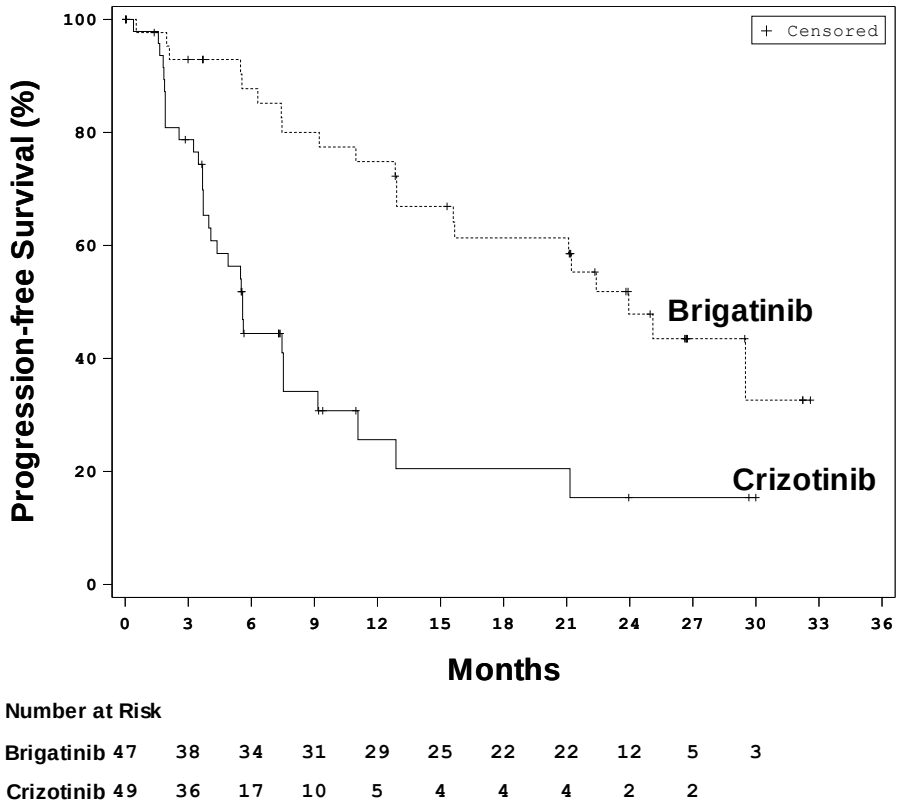
[c] measured from date of first confirmed intracranial response until date of intracranial disease progression (new intracranial lesions, intracranial target lesion diameter growth ≥ 20% from nadir, or unequivocal progression of intracranial nontarget lesions) or death or censoring

[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



In the final analysis of the 81 patients with history of brain metastasis, median overall survival was was not reached in the brigatinib arm and 37 months in the crizotinib arm (HR =0.43 [95% CI (0.21, 0.89)]).

Patient-reported symptoms, functioning and global health status (GHS)/quality of life (QOL) were measured using the EORTC QLQ-C30 and QLQ-LC13; 131 patients in the brigatinib arm and crizotinib arm, respectively, completed the EORTC QLQ-C30 at baseline and at least one post-baseline visit. Brigatinib delayed time to worsening in GHS/QOL measured by the EORTC QLQ-C30 (with worsening defined as ≥10 points worsening from baseline) compared with crizotinib (median 26.7 months versus 8.3 months; HR=0.70; 95% CI: 0.49, 1), as supported by multiple functional subscales (including physical, emotional and social), and symptom subscales (including fatigue, nausea and vomiting, appetite loss, and constipation).

ALK-Positive Advanced or Metastatic NSCLC Previously Treated with Crizotinib (ALTA, Study 201)

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 enrollment of patients with a documented ALK rearrangement based on a validated ALK test, 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 22.9 months (range: 0.1 – 39.2). 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 Tumors (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 (Table 7) 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 8 and the Kaplan-Meier (KM) curves for investigator-assessed and IRC-assessed systemic PFS are shown in Figure 3 and Figure 4 , respectively.

Table 7: Demographics and Disease Characteristics of ALK-Positive Patients treated with ALUNBRIG® in ALTA

Characteristic	90 mg qd (n=112)	90 mg → 180 mg qd* (n=110)	Total (N=222)
Sex, n (%)			
Male	50 (44.6)	46 (41.8)	96 (43.2)
Female	62 (55.4)	64 (58.2)	126 (56.8)
Age (years)			

Median (range)	51 (18-82)	57 (20-81)	54 (18-82)
Race, n (%)			
White	72 (64.3)	76 (69.1)	148 (66.7)
Asian	39 (34.8)	30 (27.3)	69 (31.1)
Other	1 (0.9)	4 (3.6)	5 (2.3)
ECOG performance status, n (%)			
0	34 (30.4)	45 (40.9)	79 (35.6)
1	71 (63.4)	56 (50.9)	127 (57.2)
2	7 (6.3)	9 (8.2)	16 (7.2)
Smoking History, n (%)			
No	71 (63.4)	63 (57.3)	134 (60.4)
Yes	40 (35.8)	47 (42.7)	87 (39.2)
Unknown	1 (0.9)	0 (0.0)	1 (0.5)
Histology, n (%)			
Adenocarinoma	107 (95.5)	108 (98.2)	215 (96.8)
Squamous	2 (1.8)	1 (0.9)	3 (1.4)
Large cell	1 (0.9)	1 (0.9)	2 (0.9)
Adenosquamous	1 (0.9)	0 (0.0)	1 (0.5)
Muciepidermoid	1 (0.9)	0 (0.0)	1 (0.5)
Brain metastases at base line n (%)			
Present	80 (71.4)	74 (67.3)	154 (69.4)
Prior chemotherapy, n (%)			
Yes	83 (74.1)	81 (73.6)	164 (73.9)
Best response to prior crizotinib, n (%)			
PR or CR	71 (63.4)	73 (66.4)	144 (64.9)
Other response or unknown	41 (36.6)	37 (33.6)	78 (35.1)

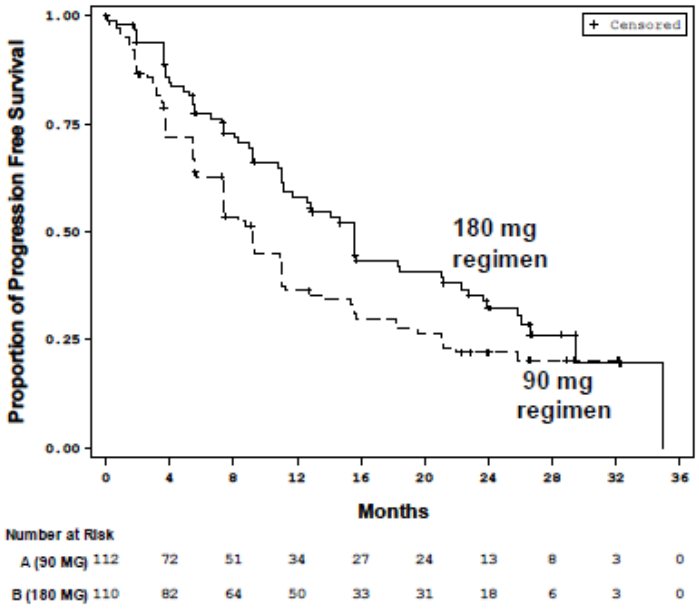
Table 8: Efficacy Results in ALTA (ITT Population)

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%	56.4%	50.9%	56.4%
CI‡	(34.8, 56.5)	(45.2, 67)	(41.3, 60.5)	(46.6, 65.8)

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

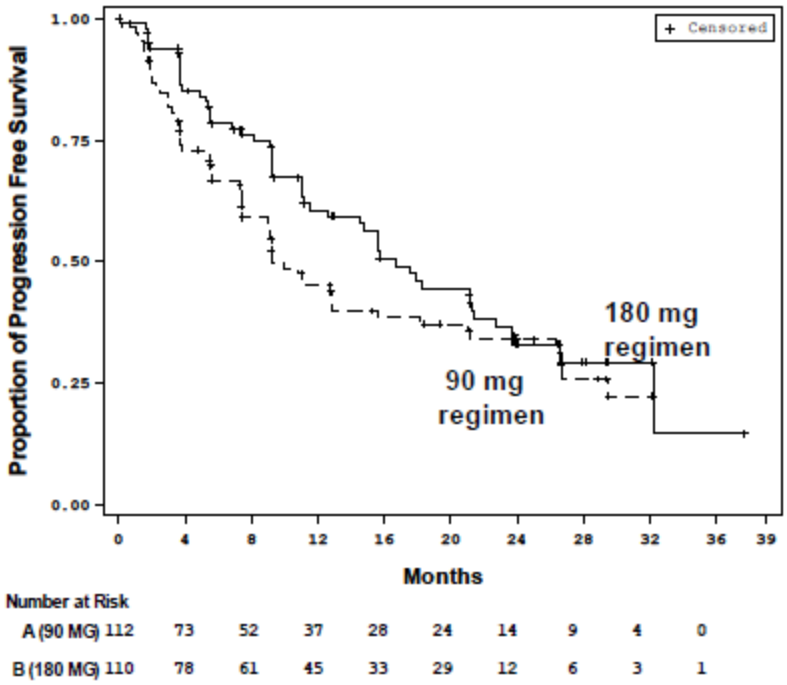
CI = Confidence Interval; NE = Not Estimable; NA = Not Applicable
*90 mg once daily regimen
†180 mg once daily with 7-day lead-in at 90 mg once daily
‡Confidence Interval for investigator-assessed ORR is 97.5% and for IRC-assessed ORR is 95%
[§] In confirmed responders

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 tumor diameters shows that the majority of patients treated with ALUNBRIG® had a reduction in tumor 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

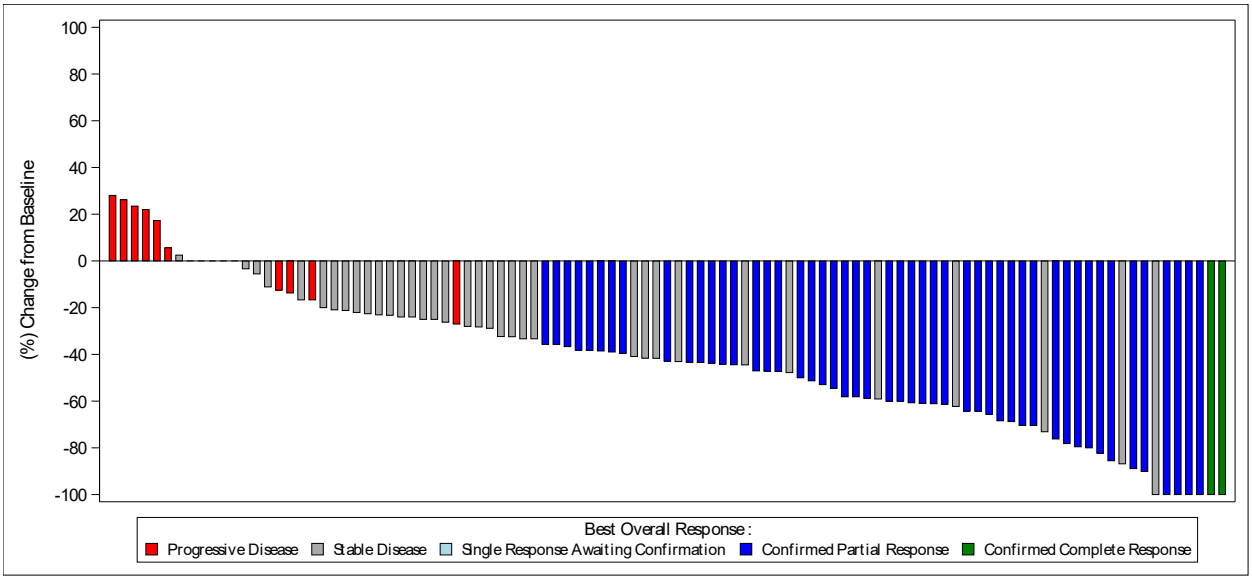
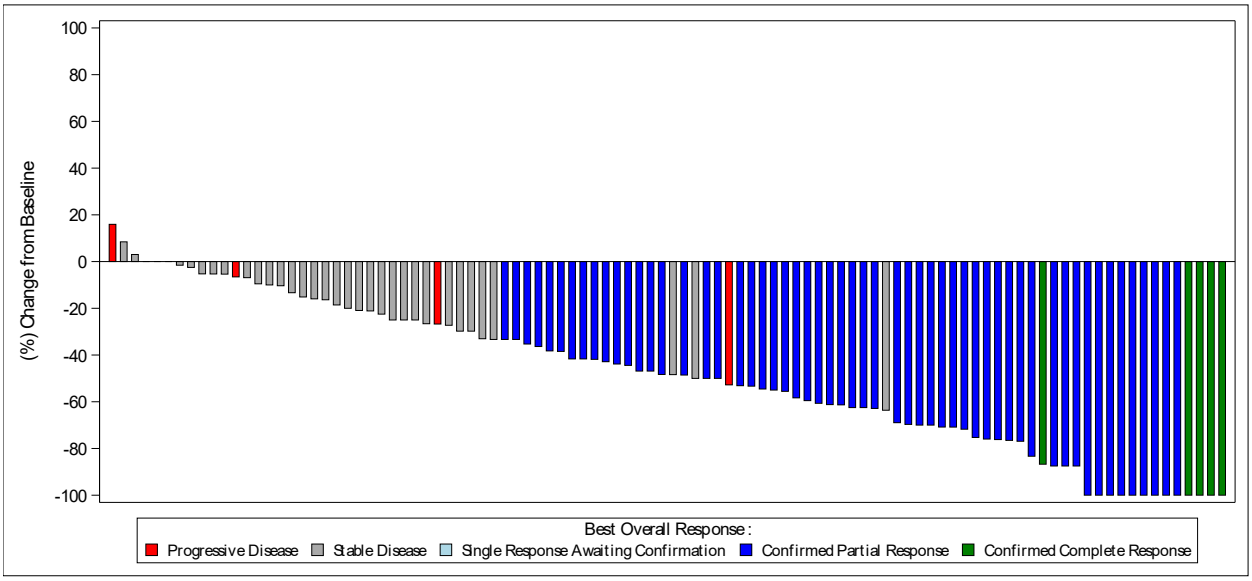


Figure 6 Waterfall Plot of Best Percent Change in Target Lesions from Baseline by Patient Based on Investigator Assessment (ALK-Positive NSCLC) – 180 mg Regimen



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 summarized in Table 9 .

Table 9: 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%	66.7%
95% CI	(29.9, 70.1)	(41, 86.7)
Intracranial Disease Control Rate		
(%)	84.6%	83.3%
95% CI	(65.1, 95.6)	(58.6, 96.4)
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 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: 22.9 months) across both dose groups.

Study 101

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) and 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 postdose. 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 is 66% bound to human plasma proteins and the binding is not concentration-dependent *in vitro*. 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 metabolized 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 and Elimination

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 feces and 25% of the administered dose was recovered in urine. Unchanged brigatinib represented 41% and 86% of the total radioactivity in feces and urine, respectively.

Special Populations

Impaired Renal Function

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)

Impaired Hepatic Function

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).

Age, Gender, Race

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

Drug Interactions

Agents that may increase brigatinib plasma concentrations

CYP3A Inhibitors

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 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 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% (e.g., 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

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-INF} by 12%, and AUC_{0-120} by 15%, relative to a 90 mg brigatinib dose administered alone. No dose adjustment is required for ALUNBRIG® 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*. 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. No dose adjustment is required for ALUNBRIG® during coadministration with P-gp and BCRP inhibitors.

Agents that may decrease brigatinib plasma concentrations

CYP3A Inducers

Coadministration of multiple 600 mg daily doses of rifampin, 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 $AUC0_{-120}$ 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 rifampin, 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 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

In vitro studies in hepatocytes have shown that brigatinib is an inducer of CYP3A. 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%, $AUC_{0\text{-}INF}$ by 26%, and $AUC_{0\text{-}last}$ by 30%, relative to a 3 mg oral dose of midazolam administered alone. Brigatinib reduces plasma concentrations of coadministered medications that are predominantly metabolized 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).

Transporter Substrates

Brigatinib is an inhibitor of P-gp, BCRP, OCT1, MATE1, and 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.

5.3 Nonclinical Safety Data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Carcinogenicity studies have not been performed with brigatinib.

Mutagenicity

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.

Impairment of Fertility

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 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.

Animal Toxicology and/or Pharmacology

Nonclinical safety assessment in rats and monkeys identified potential risk for toxicity in multiple organs such as 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

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 Special Precautions for Storage

Store below 30°C

Keep in a safe place out of the reach of and sight of children.

6.4 Nature and Contents of Container

ALUNBRIG® Film-Coated Tablets 30mg, 90mg and 180mg

Clear Thermoformable Aclar blister with Heat Sealable Paper-Laminated Foil Lidding in a carton box, containing 7 or 28 film-coated tablets.

ALUNBRIG® Initiation Pack

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

Not all presentations may be marketed.

6.5 Instructions for Use/Handling

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

7. PRODUCT OWNER

Takeda Pharmaceuticals International AG, Zurich, Switzerland

8. DATE OF REVISION

September 2021