

1 NAME OF THE MEDICINAL PRODUCT

ALUNBRIG[®] 30 MG

ALUNBRIG[®] 90 MG

Brigatinib Film-Coated Tablets, for oral use.

2 THERAPEUTIC INDICATIONS

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

3 DOSAGE AND ADMINISTRATION

3.1 Patient Selection

Select patients for the treatment of metastatic NSCLC with ALUNBRIG based on the presence of ALK positivity in tumor specimens [see *Clinical Studies (13)*].

3.2 Recommended Dosage

The recommended dosage for ALUNBRIG is:

- 90 mg orally once daily for the first 7 days; then increase the dose to 180 mg orally once daily.

Administer ALUNBRIG until disease progression or unacceptable toxicity.

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

ALUNBRIG may be taken with or without food. Instruct patients to swallow tablets whole. Do not crush or chew tablets, as the tablets are film-coated.

If a dose of ALUNBRIG is missed or vomiting occurs after taking a dose, do not administer an additional dose and take the next dose of ALUNBRIG at the scheduled time.

3.3 Dosage Modifications for Adverse Reactions

ALUNBRIG dosage reductions for adverse reactions are summarized in [Table 1](#).

Table 1: Recommended ALUNBRIG Dosage reductions

Dosage	Dosage Reduction		
	First	Second	Third
90 mg once daily	60 mg once daily	permanently discontinue	N/A [*]
180 mg once daily	120 mg once daily	90 mg once daily	60 mg once daily

^{*}Not applicable

Once reduced for adverse reactions, do not subsequently increase the dosage of ALUNBRIG. Permanently discontinue ALUNBRIG if patients are unable to tolerate the 60 mg once daily dose.

Recommendations for dosage modifications of ALUNBRIG for the management of adverse reactions are provided in [Table 2](#).

Table 2: Recommended ALUNBRIG Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modifications
Interstitial Lung Disease (ILD)/Pneumonitis <i>[see Warnings and Precautions (6.1)]</i>	Grade 1	<ul style="list-style-type: none"> • If new pulmonary symptoms occur <u>during</u> the first 7 days of treatment, withhold ALUNBRIG until recovery to baseline, then resume at same dose and do not escalate to 180 mg if ILD/pneumonitis is suspected. • If new pulmonary symptoms occur <u>after</u> the first 7 days of treatment, withhold ALUNBRIG until recovery to baseline, then resume at same dose. • If ILD/pneumonitis recurs, permanently discontinue ALUNBRIG.
	Grade 2	<ul style="list-style-type: none"> • If new pulmonary symptoms occur <u>during</u> the first 7 days of treatment, withhold ALUNBRIG until recovery to baseline. Resume at next lower dose (Table 1) and do not dose escalate if ILD/pneumonitis is suspected. • If new pulmonary symptoms occur <u>after</u> the first 7 days of treatment, withhold ALUNBRIG until recovery to baseline. If ILD/pneumonitis is suspected, resume at next lower dose (Table 1); otherwise, resume at same dose. • If ILD/pneumonitis recurs, permanently discontinue ALUNBRIG.
	Grade 3 or 4	Permanently discontinue ALUNBRIG for ILD/pneumonitis.
Hypertension <i>[see Warnings and Precautions (6.2)]</i>	Grade 3 hypertension (SBP greater than or equal to 160 mmHg or DBP greater than or equal to 100 mmHg, medical intervention indicated, more than one anti-hypertensive drug, or more intensive therapy than previously used indicated)	<ul style="list-style-type: none"> • Withhold ALUNBRIG until hypertension has recovered to Grade 1 or less (SBP less than 140 mmHg and DBP less than 90 mmHg), then resume ALUNBRIG at the same dose. • Recurrence: withhold ALUNBRIG until recovery to Grade 1 or less, and resume at next lower dose (Table 1) <u>or</u> permanently discontinue treatment.
	Grade 4 hypertension (life-threatening consequences, urgent intervention indicated)	<ul style="list-style-type: none"> • Withhold ALUNBRIG until recovery to Grade 1 or less, and resume at next lower dose (Table 1) <u>or</u> permanently discontinue treatment. • Recurrence: permanently discontinue ALUNBRIG for recurrence of Grade 4 hypertension.

Bradycardia (HR less than 60 bpm) <i>[see Warnings and Precautions (6.3)]</i>	Symptomatic bradycardia	<ul style="list-style-type: none"> • Withhold ALUNBRIG until recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above. • If a concomitant medication known to cause bradycardia is identified and discontinued or dose-adjusted, resume ALUNBRIG at same dose upon recovery to asymptomatic bradycardia or to 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 dose-adjusted, resume ALUNBRIG at next lower dose (Table 1) upon recovery to asymptomatic bradycardia or to resting heart rate of 60 bpm or above.
	Bradycardia with life-threatening consequences, urgent intervention indicated	<ul style="list-style-type: none"> • Permanently discontinue ALUNBRIG if no contributing concomitant medication is identified. • If contributing concomitant medication is identified and discontinued or dose-adjusted, resume ALUNBRIG at next lower dose (Table 1) upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above, with frequent monitoring as clinically indicated.
Visual Disturbance <i>[see Warnings and Precautions (6.4)]</i>	Grade 2 or 3 visual disturbance	Withhold ALUNBRIG until recovery to Grade 1 or baseline, then resume at the next lower dose (Table 1).
	Grade 4 visual disturbance	Permanently discontinue ALUNBRIG.
Creatine Phosphokinase (CPK) Elevation <i>[see Warnings and Precautions (6.5)]</i>	Grade 3 or 4 CPK elevation (greater than $5 \times$ ULN)	<ul style="list-style-type: none"> • Withhold ALUNBRIG until recovery to Grade 1 or less (less than or equal to $2.5 \times$ ULN) CPK elevation or to baseline, then resume ALUNBRIG at same dose. • Recurrence: Withhold ALUNBRIG until recovery to Grade 1 or less (less than or equal to $2.5 \times$ ULN) CPK elevation or to baseline, then resume ALUNBRIG at the next lower dose (Table 1).
Lipase/Amylase Elevation <i>[see Warnings and Precautions (6.6)]</i>	Grade 3 lipase or amylase elevation (greater than $2 \times$ ULN)	<ul style="list-style-type: none"> • Withhold ALUNBRIG until recovery to Grade 1 or less (less than or equal to $1.5 \times$ ULN) or to baseline, then resume ALUNBRIG at same dose. • Recurrence: Withhold ALUNBRIG until recovery to Grade 1 or less (less than or equal to $1.5 \times$ ULN) or to baseline, then resume ALUNBRIG at next lower dose (Table 1).
	Grade 4 lipase or amylase elevation (greater than $5 \times$ ULN)	Withhold ALUNBRIG until recovery to Grade 1 or less (less than or equal to $1.5 \times$ ULN) or to baseline, then resume ALUNBRIG at next lower dose (Table 1).

Hyperglycemia <i>[see Warnings and Precautions (6.7)]</i>	Grade 3 (greater than 250 mg/dL or 13.9 mmol/L) or 4	If adequate hyperglycemic control cannot be achieved with optimal medical management, withhold ALUNBRIG until adequate hyperglycemic control is achieved and resume at the next lower dose (Table 1) or permanently discontinue ALUNBRIG.
Other	Grade 3	<ul style="list-style-type: none"> • Withhold ALUNBRIG until recovery to baseline, then resume at same dose. • Recurrence: withhold ALUNBRIG until recovery to baseline, then resume at next lower dose or discontinue ALUNBRIG (Table 1).
	Grade 4	<ul style="list-style-type: none"> • Withhold ALUNBRIG until recovery to baseline and resume at next lower dose (Table 1). • Recurrence: Permanently discontinue ALUNBRIG.
bpm = beats per minute; DBP = diastolic blood pressure; HR = heart rate; 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)

3.4 Dosage Modifications for Strong or Moderate CYP3A Inhibitors

Avoid coadministration of strong or moderate CYP3A inhibitors during treatment with ALUNBRIG [see *Drug Interactions (8.1), Clinical Pharmacology (11.3)*]. If coadministration of a strong CYP3A inhibitor cannot be avoided, reduce the ALUNBRIG once daily dose by approximately 50% (i.e., from 180 mg to 90 mg, or from 90 mg to 60 mg). If coadministration of a moderate CYP3A inhibitor cannot be avoided, reduce the ALUNBRIG once daily dose by approximately 40% (i.e. from 180 mg to 120 mg, 120 mg to 90 mg, or from 90 mg to 60 mg). After discontinuation of a strong or moderate CYP3A inhibitor, resume the ALUNBRIG dose that was tolerated prior to initiating the CYP3A inhibitor.

3.5 Dosage Modifications for Moderate CYP3A Inducers

Avoid coadministration of moderate CYP3A inducers during treatment with ALUNBRIG [see *Drug Interactions (8.1), Clinical Pharmacology (11.3)*]. If coadministration of a moderate CYP3A inducer cannot be avoided, increase the ALUNBRIG once daily dose 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 initiating the moderate CYP3A inducer.

After discontinuation of a moderate CYP3A inducer, resume the ALUNBRIG dose that was tolerated prior to initiating the moderate CYP3A inducer.

3.6 Dosage Modifications for Patients with Severe Hepatic Impairment

Reduce the ALUNBRIG once daily dose by approximately 40% (i.e. from 180 mg to 120 mg, 120 mg to 90 mg, or from 90 mg to 60 mg) for patients with severe hepatic impairment (Child-Pugh C) [see *Use in Specific Populations (9.6), Clinical Pharmacology (11.3)*].

3.7 Dosage Modifications for Patients with Severe Renal Impairment

Reduce the ALUNBRIG once daily dose by approximately 50% (i.e. from 180 mg to 90 mg, or from 90 mg to 60 mg) for patients with severe renal impairment [creatinine clearance (CL_{Cr}) 15 to 29 mL/min by Cockcroft-Gault] [see *Use in Specific Populations (9.7), Clinical Pharmacology (11.3)*].

4 DOSAGE FORMS AND STRENGTHS

- 30 mg, round, white to off-white film-coated tablets with “U3” debossed on one side and plain on the other side
- 90 mg, oval, white to off-white film-coated tablets with “U7” debossed on one side and plain on the other side

5 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 10.

6 WARNINGS AND PRECAUTIONS

6.1 Interstitial Lung Disease (ILD)/Pneumonitis

Severe, life-threatening, and fatal pulmonary adverse reactions consistent with interstitial lung disease (ILD)/pneumonitis have occurred with ALUNBRIG.

In Trial ALTA 1L, ILD/pneumonitis occurred in 5.1% of patients receiving ALUNBRIG. ILD/pneumonitis occurred within 8 days of initiation of ALUNBRIG in 2.9% of patients, with Grade 3 to 4 reactions occurring in 2.2% of patients.

In Trial ALTA, ILD/pneumonitis occurred in 3.7% of patients in the 90 mg group (90 mg once daily) and 9.1% of patients in the 90→180 mg group (180 mg once daily with 7-day lead-in at 90 mg once daily).

Adverse reactions consistent with possible ILD/pneumonitis occurred within 9 days of initiation of ALUNBRIG (median onset was 2 days) in 6.4% of patients, with Grade 3 to 4 reactions occurring in 2.7%.

Monitor for new or worsening respiratory symptoms (e.g., dyspnea, cough, etc.), particularly during the first week of

initiating ALUNBRIG. Withhold ALUNBRIG in any patient with new or worsening respiratory symptoms, and promptly evaluate for ILD/pneumonitis or other causes of respiratory symptoms (e.g., pulmonary embolism, tumor progression, and infectious pneumonia). For Grade 1 or 2 ILD/pneumonitis, either resume ALUNBRIG with dose reduction according to [Table 1](#) after recovery to baseline or permanently discontinue ALUNBRIG. Permanently discontinue ALUNBRIG for Grade 3 or 4 ILD/pneumonitis or recurrence of Grade 1 or 2 ILD/pneumonitis [*see Dosage and Administration (3.3), Adverse Reactions (7)*].

6.2 Hypertension

In ALTA 1L, hypertension was reported in 32% of patients receiving ALUNBRIG; Grade 3 hypertension occurred in 13% of patients.

In ALTA, hypertension was reported in 11% of patients in the 90 mg group who received ALUNBRIG and 21% of patients in the 90→180 mg group. Grade 3 hypertension occurred in 5.9% of patients overall.

Control blood pressure prior to treatment with ALUNBRIG. Monitor blood pressure after 2 weeks and at least monthly thereafter during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 hypertension despite optimal antihypertensive therapy. Upon resolution or improvement to Grade 1, resume ALUNBRIG at the same dose. Consider permanent discontinuation of treatment with ALUNBRIG for Grade 4 hypertension or recurrence of Grade 3 hypertension [*see Dosage and Administration (3.3), Adverse Reactions (7)*].

Use caution when administering ALUNBRIG in combination with antihypertensive agents that cause bradycardia [*see Warnings and Precautions (6.3)*].

6.3 Bradycardia

In ALTA 1L, heart rates less than 50 beats per minute (bpm) occurred in 8.1% of patients receiving ALUNBRIG. Grade 3 bradycardia occurred in 1 patient (0.7%).

In ALTA, heart rates less than 50 beats per minute (bpm) occurred in 5.7% of patients in the 90 mg group and 7.6% of patients in the 90→180 mg group. Grade 2 bradycardia occurred in 1 (0.9%) patient in the 90 mg group.

Monitor heart rate and blood pressure during treatment with ALUNBRIG. Monitor patients more frequently if concomitant use of drug known to cause bradycardia cannot be avoided [*see Warnings and Precautions (56.2)*].

For symptomatic bradycardia, withhold ALUNBRIG and review concomitant medications for those known to cause bradycardia. If a concomitant medication known to cause bradycardia is identified and discontinued or dose adjusted, resume ALUNBRIG at the same dose following resolution of symptomatic bradycardia; otherwise, reduce the dose of ALUNBRIG following resolution of symptomatic bradycardia. Discontinue ALUNBRIG for life-threatening bradycardia if no contributing concomitant medication is identified [*see Dosage and Administration (3.3)*].

6.4 Visual Disturbance

In ALTA 1L, Grade 1 or 2 adverse reactions leading to visual disturbance including blurred vision, photophobia, photopsia, and reduced visual acuity were reported in 7.4% of patients receiving ALUNBRIG.

In ALTA, adverse reactions leading to visual disturbance including blurred vision, diplopia, and reduced visual acuity, were reported in 7.3% of patients receiving ALUNBRIG in the 90 mg group and 10% of patients in the 90→180 mg group. Grade 3 macular edema and cataract occurred in 1 patient each in the 90→180 mg group.

Advise patients to report any visual symptoms. Withhold ALUNBRIG and obtain an ophthalmologic evaluation in patients with new or worsening visual symptoms of Grade 2 or greater severity. Upon recovery of Grade 2 or Grade 3 visual disturbances to Grade 1 severity or baseline, resume ALUNBRIG at a reduced dose. Permanently discontinue treatment with ALUNBRIG for Grade 4 visual disturbances [*see Dosage and Administration (3.3), Adverse Reactions (7)*].

6.5 Creatine Phosphokinase (CPK) Elevation

In ALTA 1L, creatine phosphokinase (CPK) elevation occurred in 81% of patients who received ALUNBRIG. The incidence of Grade 3 or 4 CPK elevation was 24%. Dose reduction for CPK elevation occurred in 15% of patients.

In ALTA, CPK-elevation occurred in 27% of patients receiving ALUNBRIG in the 90 mg group and 48% of patients in the 90 mg→180 mg group. The incidence of Grade 3-4 CPK elevation was 2.8% in the 90 mg group and 12% in the 90→180 mg group.

Dose reduction for CPK elevation occurred in 1.8% of patients in the 90 mg group and 4.5% in the 90→180 mg group. Advise patients to report any unexplained muscle pain, tenderness, or weakness. Monitor CPK levels during ALUNBRIG treatment. Withhold ALUNBRIG for Grade 3 or 4 CPK elevation. Upon resolution or recovery to Grade 1 CPK elevation or baseline, resume ALUNBRIG at the same dose or at a reduced dose as described in [Table 2](#) [see *Dosage and Administration* (3), *Adverse Reactions* (7)].

6.6 Pancreatic Enzymes Elevation

In ALTA 1L, amylase elevation occurred in 52% of patients and Grade 3 or 4 amylase elevation occurred in 6.8% of patients. Lipase elevations occurred in 59% of patients and Grade 3 or 4 lipase elevation occurred in 17% of patients.

In ALTA, amylase elevation occurred in 27% of patients in the 90 mg group and 39% of patients in the 90→180 mg group. Lipase elevations occurred in 21% of patients in the 90 mg group and 45% of patients in the 90→180 mg group. Grade 3 or 4 amylase elevation occurred in 3.7% of patients in the 90 mg group and 2.7% of patients in the 90→180 mg group. Grade 3 or 4 lipase elevation occurred in 4.6% of patients in the 90 mg group and 5.5% of patients in the 90→180 mg group.

Monitor lipase and amylase during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 or 4 pancreatic enzyme elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose as described in [Table 2](#) [see *Dosage and Administration* (3.3), *Adverse Reactions* (7)].

6.7 Hyperglycemia

In ALTA 1L, 56% of patients who received ALUNBRIG experienced new or worsening hyperglycemia. Grade 3 hyperglycemia, based on laboratory assessment of serum fasting glucose levels, occurred in 7.5% of patients.

In ALTA, 43% of patients who received ALUNBRIG experienced new or worsening hyperglycemia. Grade 3 hyperglycemia, based on laboratory assessment of serum fasting glucose levels, occurred in 3.7% of patients. Two of 20 (10%) patients with diabetes or glucose intolerance at baseline required initiation of insulin while receiving ALUNBRIG.

Assess fasting serum glucose prior to initiation of ALUNBRIG and monitor periodically thereafter. Initiate or optimize anti-hyperglycemic medications as needed. If adequate hyperglycemic control cannot be achieved with optimal medical management, withhold ALUNBRIG until adequate hyperglycemic control is achieved and consider reducing the dose of ALUNBRIG as described in [Table 1](#) or permanently discontinuing ALUNBRIG [see *Dosage and Administration* (3), *Adverse Reactions* (7)].

6.8 Photosensitivity

In ALTA 1L, photosensitivity occurred in 3.7% of patients who received ALUNBRIG, with 0.7% Grade 3 to 4.

In ALTA, 0.9% of patients who received ALUNBRIG in the 90 mg group experienced photosensitivity and 0.9% of patients in the 90 mg→180 mg group. Grade 3 to 4 photosensitivity was not reported in patients in the 90 mg group or in the 90→180 mg group.

Advise patients to limit sun exposure while taking brigatinib, and for at least 5 days after discontinuation of treatment. Advise patients, when outdoors to wear a hat and protective clothing, and use a broad-spectrum Ultraviolet A (UVA)/ Ultraviolet B (UVB) sunscreen and lip balm (SPF ≥30) to help protect against sunburn. Based on the severity withhold ALUNBRIG, then resume at the same dose, or reduce the dose, or permanently discontinue as described in [Table 2](#) [see *Dosage and Administration* (2.3), *Adverse Reactions* (6.1)].

6.9 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. Administration of

brigatinib to pregnant rats during the period of organogenesis resulted in dose-related skeletal anomalies at doses as low as 12.5 mg/kg/day (approximately 0.7 times the human exposure by AUC at 180 mg once daily) as well as increased post implantation loss, malformations, and decreased fetal body weight at doses of 25 mg/kg/day (approximately 1.26 times the human exposure at 180 mg once daily) or higher.

Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ALUNBRIG and for at least 4 months following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for at least 3 months after the last dose of ALUNBRIG [*see Use in Specific Populations (9.1, 9.3), Clinical Pharmacology (11.3)*].

6.10 Lactose & Sodium

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.

Alunbrig also contains Sodium.

7 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the prescribing information:

- Interstitial Lung Disease (ILD)/Pneumonitis [*see Warnings and Precautions (6.1)*]
- Hypertension [*see Warnings and Precautions (6.2)*]
- Bradycardia [*see Warnings and Precautions (6.3)*]
- Visual Disturbance [*see Warnings and Precautions (6.4)*]
- Creatine Phosphokinase (CPK) Elevation [*see Warnings and Precautions (6.5)*]
- Pancreatic Enzymes Elevation [*see Warnings and Precautions (6.6)*]
- Hyperglycemia [*see Warnings and Precautions (6.7)*]
- Photosensitivity [*see Warnings and Precautions (6.8)*]

7.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Advanced ALK-positive NSCLC Without Prior ALK-targeted Therapy

In ALTA 1L, the safety of ALUNBRIG was evaluated in 136 patients with advanced ALK-positive NSCLC who had not previously received an ALK-targeted therapy [*see Clinical Studies (13)*]. The median duration of treatment with ALUNBRIG when administered as 90 mg orally once daily for the first 7 days; then increased to 180 mg orally once daily, was 24.3 months. A total of 106 (78%) patients were exposed to ALUNBRIG for greater than or equal to 6 months including 92 (68%) patients exposed for greater than or equal to 1 year. The median relative dose intensity was 97% for ALUNBRIG.

The study population (N = 275) characteristics were: median age 59 years (range: 27 to 89), age less than 65 years (68%), female (55%), White (59%), Asian (39%), Stage IV disease (93%), NSCLC adenocarcinoma histology (96%), never smoker (58%), ECOG Performance Status (PS) 0 or 1 (95%), and CNS metastases at baseline (30%) [*see Clinical Studies (13)*].

Serious adverse reactions occurred in 33% of patients receiving ALUNBRIG. The most common serious adverse reactions were pneumonia (4.4%), ILD/pneumonitis (3.7%), pyrexia (2.9%), dyspnea (2.2%), pulmonary embolism (2.2%), and asthenia (2.2%). Fatal adverse reactions occurred in 2.9% of patients and included pneumonia (1.5%), cerebrovascular accident (0.7%), and multiple organ dysfunction syndrome (0.7%).

In ALTA 1L, 13% of patients receiving ALUNBRIG permanently discontinued ALUNBRIG for adverse reactions. The most frequent adverse reactions that led to discontinuation were ILD/pneumonitis (3.7%) and pneumonia (2.2%). In ALTA 1L, 38% of patients required a dose reduction due to adverse reactions. The most common adverse reaction that led to dose reduction was increased creatine phosphokinase (15%), increased lipase (6.6%), increased amylase (4.4%), increased aspartate aminotransferase (2.2%), ILD/pneumonitis (2.2%) and hypertension (2.2%).

Table 3 and Table 4 summarize the common adverse reactions and laboratory abnormalities observed in ALTA 1L.

Table 3: Adverse Reactions in $\geq 10\%$ (All Grades*) or $\geq 2\%$ (Grades 3-4) of Patients by Arm in ALTA 1L (N = 273)

Adverse Reactions	ALUNBRIG N = 136		Crizotinib N = 137	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal Disorders				
Diarrhea	53	2.2	57	2.9
Nausea	30	2.2	58	2.9
Abdominal pain [†]	24	0.7	33	3.6
Vomiting	21	0.7	44	2.2
Constipation	18	0	42	0
Stomatitis [‡]	13	0.7	8.8	0
Dyspepsia	8	0	16	0.7
Gastroesophageal reflux disease	0.7	0	11	0
Skin and Subcutaneous Tissue Disorders				
Rash [§]	40	2.9	17	0
Pruritus [¶]	20	0.7	5.8	0.7
Respiratory, Thoracic and Mediastinal Disorders				
Cough	35	0	20	0
Dyspnea [#]	25	2.9	22 ^D	3.6
ILD/Pneumonitis	5.1	2.9	2.2	0.7
Pulmonary embolism	2.2	2.2	5.8 ^D	2.9
Vascular Disorders				
Hypertension ^P	32	13	8	2.9
General Disorders and Administration Site Conditions				
Fatigue ^B	32	1.5	40	2.2
Edema ^A	18	0.7	48	0.7
Pyrexia	15	0.7	15	0
Musculoskeletal and Connective Tissue Disorders				
Myalgia ^C	28	0	23	0
Back pain	21	0.7	17	1.5
Arthralgia	14	0	12	0
Pain in extremity	5.1	0	15	0.7
Nervous System Disorders				
Headache ^O	22	2.2	17	0
Dizziness	15	0.7	20	0.7
Peripheral neuropathy ^Q	11	0.7	18	0
Dysgeusia	2.9	0	14	0
Investigations				
Increased Blood cholesterol ^V	13	0	0.7	0
Cardiac Disorders				
Bradycardia ^K	12	0.7	23	0
Infections and Infestations				
Pneumonia ^Y	15 ^D	5.1	6.6 ^D	2.9
Upper respiratory tract infection ^{OE}	12	0	10	0
Nasopharyngitis	8	0	11	0

Urinary tract infection	5.9	0.7	8.8	2.2
Metabolism and Nutrition Disorders				
Decreased Appetite	8.8	0.7	19	2.9
Eye Disorders				
Visual Disturbance ^{oe}	7.4	0	53	0.7

* Per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03

† Includes abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper, and epigastric discomfort

‡ Includes aphthous ulcer, mouth ulceration, oral mucosal blistering and stomatitis

§ Includes dermatitis, dermatitis acneiform, dermatitis bullous, dermatitis contact, drug eruption, erythema, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, toxic skin eruption, urticaria

¶ Includes pruritus, allergic pruritus, and generalized pruritus

Includes dyspnea and exertional dyspnea

Ⓟ Includes hypertension and systolic hypertension

â Includes asthenia and fatigue

à Includes angioedema, eye swelling, eyelid edema, face edema, generalized edema, lip swelling, peripheral edema, periorbital edema, peripheral swelling, skin swelling, swelling and swelling face

ê Includes muscle spasms, muscle twitching, musculoskeletal discomfort, musculoskeletal pain, and myalgia

ð Includes headache and migraine

º Includes burning sensation, dysesthesia, hyperesthesia, hypoesthesia, neuralgia, peripheral neuropathy, paraesthesia, peripheral sensory neuropathy and polyneuropathy

ÿ Includes blood cholesterol increased, hypercholesterolaemia

£ Includes bradycardia, heart rate decreased, sinus bradycardia

¥ Includes lower respiratory tract infection, lung infection, pneumonia, aspiration pneumonia, and cryptococcal pneumonia

^{OE} Includes upper respiratory tract infection and viral upper respiratory tract infection

^{oe} Includes cataract, glaucoma, hypermetropia, night blindness, papilloedema, photophobia, photopsia, blurred vision, reduced visual acuity, visual field defect, visual impairment, and vitreous floaters

^D Includes Grade 5 events

Table 4: Laboratory Abnormalities in $\geq 20\%$ (All Grades*) of Patients by Arm in ALTA 1L (N = 273)				
Laboratory Abnormality	ALUNBRIG N = 136**		Crizotinib N = 137**	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Chemistry				
Increased creatine phosphokinase	81	24	68	4.8
Increased aspartate aminotransferase	72	4.5	70	5.2
Increased lipase	59	17	36	9.8
Hyperglycemia [†]	56	7.5	37	3.7
Increased alanine aminotransferase	52	5.2	77	13
Increased amylase	52	6.8	25	3
Decreased phosphorous	41	3.7	39	6
Increased alkaline phosphatase	36	3	49	1.5
Increased creatinine	25	0	33	0
Potassium increased	24	1.5	31	3.7
Increased calcium	22	0	1.5	0
Decreased magnesium	21	0	6.9	0
Decreased albumin	15	0.8	52	3.7
Decreased calcium	15	0	67	1.5
Hematology				
Hemoglobin decreased	41	2.3	36	1.5
Lymphocyte count decreased	42	9.3	30	5.4
Neutrophil count decreased	12	0	34	6.8

* Per CTCAE version 4.03

** Denominator for each laboratory parameter may vary and is defined as the number of patients who had both, baseline and post-baseline test

† Elevated blood insulin was also observed in both arms

Clinically relevant adverse reactions in patients who received ALUNBRIG included photosensitivity (3.7%).

ALK-positive Advanced or Metastatic NSCLC Previously Treated with Crizotinib

The safety of ALUNBRIG was evaluated in 219 patients with locally advanced or metastatic ALK-positive NSCLC who received at least 1 dose of ALUNBRIG in ALTA after experiencing disease progression on crizotinib. Patients received ALUNBRIG 90 mg once daily continuously (90 mg group) or 90 mg once daily for 7 days followed by 180 mg once daily (90→180 mg group). The median duration of treatment was 7.5 months in the 90 mg group and 7.8 months in the 90→180 mg group. A total of 150 (68%) patients were exposed to ALUNBRIG for greater than or equal to 6 months and 42 (19%) patients were exposed for greater than or equal to 1 year.

The study population (N=222) characteristics were: median age 54 years (range: 18 to 82), age less than 65 years (77%), female (57%), White (67%), Asian (31%), Stage IV disease (98%), NSCLC adenocarcinoma histology (97%), never or former smoker (95%), ECOG Performance Status (PS) 0 or 1 (93%), and CNS metastases at baseline (69%) [see *Clinical Studies (13)*].

Serious adverse reactions occurred in 38% of patients in the 90 mg group and 40% of patients in the 90→180 mg group. The most common serious adverse reactions were pneumonia (5.5% overall, 3.7% in the 90 mg group, and 7.3% in the

90→180 mg group) and ILD/pneumonitis (4.6% overall, 1.8% in the 90 mg group and 7.3% in the 90→180 mg group). Fatal adverse reactions occurred in 3.7% of patients and consisted of pneumonia (2 patients), sudden death, dyspnea, respiratory failure, pulmonary embolism, bacterial meningitis and urosepsis (1 patient each).

In ALTA, 2.8% of patients in the 90 mg group and 8.2% of patients in the 90→180 mg group permanently discontinued ALUNBRIG for adverse reactions. The most frequent adverse reactions that led to discontinuation were ILD/pneumonitis (0.9% in the 90 mg group and 1.8% in the 90→180 mg group) and pneumonia (1.8% in the 90→180 mg group only).

In ALTA, 14% of patients required a dose reduction due to adverse reactions (7.3% in the 90 mg group and 20% in the 90→180 mg group). The most common adverse reaction that led to dose reduction was increased creatine phosphokinase for both regimens (1.8% in the 90 mg group and 4.5% in the 90→180 mg group).

Table 5 and Table 6 summarize the common adverse reactions and laboratory abnormalities observed in ALTA.

Adverse Reactions	90 mg once daily N =		90→180 mg once daily N = 110	
	All Grade	Grades 3-4 (%)	All Grade	Grades 3-4 (%)
Gastrointestinal Disorders				
Nausea	33	0.9	40	0.9
Diarrhea	19	0	38	0
Vomiting	24	1.8	23	0
Constipation	19	0.9	15	0
Abdominal Pain [†]	17	0	10	0
General Disorders and Administration Site Conditions				
Fatigue [‡]	29	1.8	36	0
Pyrexia	14	0	6.4	0.9
Respiratory, Thoracic and Mediastinal Disorders				
Cough	18	0	34	0
Dyspnea [§]	27	2.8	21	1.8 ^{††}
ILD/Pneumonitis	3.7	1.8	9.1	2.7
Hypoxia	0.9	0	2.7	2.7
Nervous System Disorders				
Headache [¶]	28	0	27	0.9
Peripheral Neuropathy [#]	13	0.9	13	1.8
Skin and Subcutaneous Tissue Disorders				
Rash ^P	15	1.8	24	3.6
Vascular Disorders				
Hypertension	11	5.5	21	6.4
Musculoskeletal and Connective Tissue Disorders				
Muscle Spasms	12	0	17	0
Back pain	10	1.8	15	1.8
Myalgia ^{**}	9.2	0	15	0.9
Arthralgia	14	0.9	14	0
Pain in extremity	11	0	3.6	0.9
Metabolism and Nutrition Disorders				
Decreased Appetite	22	0.9	15	0.9

Eye Disorders				
Visual Disturbance ^{††}	7.3	0	10	0.9
Infections				
Pneumonia	4.6	2.8 ^{†††}	10	5.5 ^{†††}
Psychiatric Disorders				
Insomnia	11	0	7.3	0

*Per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

†Includes abdominal distension, abdominal pain, and epigastric discomfort

‡Includes asthenia and fatigue

§Includes dyspnea and exertional dyspnea

#Includes headache and sinus headache

¶Includes peripheral sensory neuropathy and paresthesia

ⓂIncludes acneiform dermatitis, exfoliative rash, rash, pruritic rash, and pustular rash

**Includes musculoskeletal pain and myalgia

††Includes diplopia, photophobia, blurred vision, reduced visual acuity, visual impairment, vitreous floaters, visual field defect, macular edema, and vitreous detachment

†††Includes one Grade 5 event

Table 6: Laboratory Abnormalities in ≥20% (All Grades*) of Patients by Regimen in ALTA (N=219)				
Laboratory Abnormality	90 mg once daily N=		90→180 mg once daily N=110	
	All Grade	Grades 3-4 (%)	All Grade	Grades 3-4 (%)
Chemistry				
Increased aspartate aminotransferase	38	0.9	65	0
Hyperglycemia [†]	38	3.7	49	3.6
Increased creatine phosphokinase	27	2.8	48	12
Increased lipase	21	4.6	45	5.5
Increased alanine aminotransferase	34	0	40	2.7
Increased amylase	27	3.7	39	2.7
Increased alkaline phosphatase	15	0.9	29	0.9
Decreased phosphorous	15	1.8	23	3.6
Prolonged activated partial thromboplastin time	22	1.8	20	0.9
Hematology				
Anemia	23	0.9	40	0.9
Lymphopenia	19	2.8	27	4.5

*Per CTCAE version 4.0

†Elevated blood insulin was observed in both regimens

Clinically relevant adverse reactions in patients who received ALUNBRIG included photosensitivity (0.9%).

Other Adverse Reactions from Multiple Clinical Trials

In a pooled clinical trial population consisting of three studies with 274 patients treated with ALUNBRIG at the recommended dose, the following adverse reactions and laboratory abnormalities were reported: white blood cell count decreased (28%), hyponatremia (20%), hypokalemia (19%), decreased platelet count (10%), dry skin (4.7%), pain (3.3%), and musculoskeletal stiffness (1.1%).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il>

8 DRUG INTERACTIONS

8.1 Effect of Other drugs on ALUNBRIG

Strong or Moderate CYP3A Inhibitors

Co-administration of ALUNBRIG with a strong or moderate CYP3A inhibitor increased brigatinib plasma concentrations, which may increase the incidence of adverse reactions [see *Clinical Pharmacology (11.3)*]. Avoid coadministration of ALUNBRIG with strong or moderate CYP3A inhibitors. If coadministration of strong or moderate CYP3A inhibitors cannot be avoided, modify dose as recommended [see *Dosage and Administration (3.4)*].

Strong or Moderate CYP3A Inducers

Co-administration of ALUNBRIG with a strong or moderate CYP3A inducer decreased brigatinib plasma concentrations, which may decrease the efficacy of ALUNBRIG [see *Clinical Pharmacology (11.3)*]. Avoid coadministration of ALUNBRIG with strong or moderate CYP3A inducers. If coadministration of moderate CYP3A inducers cannot be avoided, modify dose as recommended [see *Dosage and Administration (3.5)*].

9 USE IN SPECIFIC POPULATIONS

9.1 Pregnancy

Risk Summary

Based on its mechanism of action and findings in animals, ALUNBRIG can cause fetal harm when administered to a pregnant woman

[see *Clinical Pharmacology (11.1)*]. There are no clinical data on the use of ALUNBRIG in pregnant women. Administration of brigatinib to pregnant rats during the period of organogenesis resulted in dose-related skeletal anomalies at doses as low as 12.5 mg/kg/day (approximately 0.7 times the human exposure by AUC at 180 mg once daily) as well as increased post-implantation loss, malformations, and decreased fetal body weight at doses of 25 mg/kg/day (approximately 1.26 times the human exposure at 180 mg once daily) or greater (see *Data*). Advise pregnant women of the potential risk to a fetus.

Data

Animal Data

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.

9.2 Lactation

Risk Summary

There are no data regarding the secretion of brigatinib in human milk or its effects on the breastfed infant or milk production. Because of the potential for adverse reactions in breastfed infants, advise lactating women not to breastfeed during treatment with ALUNBRIG and for 1 week following the final dose.

9.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating ALUNBRIG [see *Use in Specific Populations (9.1)*].

Contraception

ALUNBRIG can cause fetal harm [see *Use in Specific Populations (9.1)*].

Females

Advise females of reproductive potential to use effective contraception during treatment with ALUNBRIG and for at least 4 months after the final dose.

Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with ALUNBRIG and for at least 3 months after the final dose [see *Nonclinical Toxicology (12.1)*].

Infertility

Based on findings in male reproductive organs in animals, ALUNBRIG may cause reduced fertility in males [see *Nonclinical Toxicology (12.1)*].

9.4 Pediatric Use

The safety and effectiveness of ALUNBRIG in pediatric patients have not been established.

9.5 Geriatric Use

Of the 359 patients enrolled in the ALTA 1L ALUNBRIG arm and in ALTA, 26.7% were 65 and older and 7.5% were 75 and older. No overall differences in safety or effectiveness were observed between patients ≥ 65 years and younger patients.

9.6 Hepatic Impairment

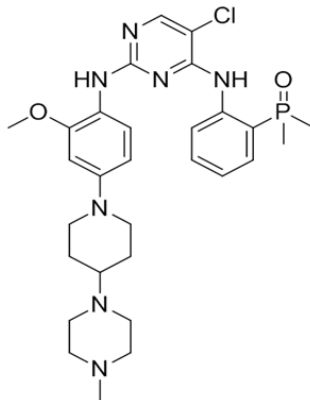
No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A) or moderate hepatic impairment (Child-Pugh B). Reduce the dose of ALUNBRIG for patients with severe hepatic impairment (Child-Pugh C) [see *Dosage and administration (3.6), Clinical Pharmacology (11.3)*].

9.7 Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment [creatinine clearance (CL_{cr}) 30 to 89 mL/min by Cockcroft-Gault]. Reduce the dose of ALUNBRIG for patients with severe renal impairment (CL_{cr} 15 to 29 mL/min) [see *Dosage and Administration (3.7), Clinical Pharmacology (11.3)*].

10 DESCRIPTION

Brigatinib is a kinase inhibitor. The chemical name for brigatinib is 5-chloro-N⁴-[2-(dimethylphosphoryl)phenyl]-N²-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-2,4-diamine. The molecular formula is C₂₉H₃₉N₇O₂P 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).

ALUNBRIG is supplied for oral use as film-coated tablets containing 30 mg or 90 mg of brigatinib and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, sodium starch glycolate (Type A), magnesium stearate, and hydrophobic colloidal silica. The tablet coating consists of talc, polyethylene glycol, polyvinyl alcohol, and titanium dioxide.

11 CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

Brigatinib is a tyrosine kinase inhibitor with *in vitro* activity at clinically achievable concentrations against multiple kinases including ALK, ROS1, insulin-like growth factor-1 receptor (IGF-1R), and FLT-3 as well as EGFR deletion and point mutations. Brigatinib inhibited autophosphorylation of ALK and ALK-mediated phosphorylation of the downstream signaling proteins STAT3, AKT, ERK1/2, and S6 in *in vitro* and *in vivo* assays. Brigatinib also 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 clinically achievable concentrations (≤ 500 nM), brigatinib inhibited the *in vitro* viability of cells expressing EML4-ALK and 17 mutant forms associated with resistance to ALK inhibitors including crizotinib, as well as EGFR-Del (E746-A750), ROS1-L2026M, FLT3-F691L, and FLT3-D835Y. Brigatinib exhibited *in vivo* anti-tumor activity against 4 mutant forms of EML4-ALK, including G1202R and L1196M mutants identified in NSCLC tumors in patients who have progressed on crizotinib. Brigatinib also reduced tumor burden and prolonged survival in mice implanted intracranially with an ALK-driven tumor cell line.

11.2 Pharmacodynamics

Brigatinib exposure-response relationships and the time course of the pharmacodynamic response are unknown.

Cardiac Electrophysiology

The QT interval prolongation potential of ALUNBRIG was assessed in 123 patients following once daily ALUNBRIG doses of 30 mg (0.16 times the recommended dose of 180 mg) to 240 mg (1.3 times the recommended dose of 180 mg). ALUNBRIG did not prolong the QT interval to a clinically relevant extent.

11.3 Pharmacokinetics

The geometric mean (CV%) steady-state maximum concentration (C_{max}) of brigatinib at ALUNBRIG doses of 90 mg and 180 mg once daily was 552 (49%) ng/mL and 1452 (60%) ng/mL, respectively, and the corresponding area under the concentration-time curve (AUC_{0-Tau}) was 8165 (45%) ng·h/mL and 20276 (62%) ng·h/mL. After a single dose and multiple dosing of ALUNBRIG, systemic exposure of brigatinib was dose proportional over the dose range of 60 mg (0.3 times the recommended dose of 180 mg) to 240 mg (1.3 times the recommended dose of 180 mg) once daily. The mean accumulation ratio after repeat dosing was 1.9 to 2.4.

Absorption

Following administration of single oral doses of ALUNBRIG of 30 mg to 240 mg, the median time to peak concentration (T_{max}) ranged from 1 to 4 hours.

Effect of Food

Brigatinib C_{max} was reduced by 13% with no effect on AUC in healthy subjects administered ALUNBRIG after a high fat meal (approximately 920 calories, 58 grams carbohydrate, 59 grams fat and 40 grams protein) compared to the C_{max} and AUC after overnight fasting.

Distribution

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

Elimination

Following oral administration of ALUNBRIG 180 mg once daily, the mean apparent oral clearance (CL/F) of brigatinib at steady-state is 8.9 L/h and the mean plasma elimination half-life is 25 hours.

Metabolism

Brigatinib is primarily metabolized by CYP2C8 and CYP3A4 in vitro. Following oral administration of a single 180 mg dose of radiolabeled brigatinib to healthy subjects, N-demethylation and cysteine conjugation were the two major metabolic pathways. Unchanged brigatinib (92%) was the major circulating radioactive component.

Excretion

Following oral administration of a single 180 mg dose of radiolabeled brigatinib to healthy 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.

Specific Populations

Age, race, sex, body weight, and albumin concentration have no clinically meaningful effect on the pharmacokinetics of brigatinib.

Patients with Hepatic Impairment

Following a single dose of ALUNBRIG 90 mg, unbound brigatinib systemic exposure (AUC_{0-Inf}) was 37% higher in subjects with severe hepatic impairment (Child-Pugh C) compared to subjects with normal hepatic function. Unbound brigatinib systemic exposure (AUC_{0-Inf}) was similar between subjects with mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment and subjects with normal hepatic function [*see Dosage and Administration (3.6)*].

Patients with Renal Impairment

Following a single dose of ALUNBRIG 90 mg, unbound brigatinib systemic exposure (AUC_{0-Inf}) was 86% higher in subjects with severe renal impairment [creatinine clearance (CL_{Cr}) 15 to 29 mL/min] compared to subjects with normal renal function.

Based on a population pharmacokinetic analysis, brigatinib exposures were similar among 125 subjects with mild renal impairment (CL_{Cr} 60 to 89 mL/min), 34 subjects with moderate renal impairment (CL_{Cr} 30 to 59 mL/min) and 270 subjects with normal renal function ($CL_{Cr} \geq 90$ mL/min) [*see Dosage and Administration (3.7)*].

Drug Interaction Studies

Clinical Studies

Effect of Strong and Moderate CYP3A Inhibitors on Brigatinib:

Co-administration of 200 mg twice daily doses of itraconazole (a strong CYP3A inhibitor) with a single 90 mg

dose of ALUNBRIG increased brigatinib C_{max} by 21% and AUC_{0-12h} by 101%, relative to a 90 mg dose of ALUNBRIG administered alone [see Dosage and Administration (3), Drug Interactions (8.1)]. A moderate CYP3A inhibitor is predicted to increase the AUC of brigatinib by approximately 40%.

Effect of Strong CYP2C8 Inhibitors in Brigatinib:

Co-administration of 600 mg twice daily doses of gemfibrozil (a strong CYP2C8 inhibitor) with a single 90 mg dose of ALUNBRIG decreased brigatinib C_{max} by 41% and AUC_{0-12h} by 12%, relative to a 90 mg dose of ALUNBRIG 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.

Effect of Strong and Moderate CYP3A Inducers on Brigatinib:

Co-administration of 600 mg daily doses of rifampin (a strong CYP3A inducer) with a single 180 mg dose of ALUNBRIG decreased brigatinib C_{max} by 60% and AUC_{0-12h} by 80%, relative to a 180 mg dose of ALUNBRIG administered alone [see Dosage and Administration (3.5), Drug Interactions (8.1)]. A moderate CYP3A inducer is predicted to decrease the AUC of brigatinib by approximately 50%.

Effect of Brigatinib on CYP3A Substrates:

Coadministration of 180 mg daily doses of ALUNBRIG with a single 3 mg oral dose of midazolam (a sensitive CYP3A substrate) decreased midazolam C_{max} by 16% and AUC_{0-12h} by 26%, relative to a 3 mg oral dose of midazolam administered alone. Brigatinib is considered a weak inducer of CYP3A.

In Vitro Studies

Effect of Brigatinib on CYP Enzymes:

Brigatinib, at clinically relevant plasma concentrations, induced CYP3A via activation of the pregnane X receptor (PXR). Brigatinib may also induce CYP2C enzymes via the same mechanism at clinically relevant concentrations. Brigatinib did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5 at clinically relevant concentrations.

Effect of P-glycoprotein and BCRP Inhibitors on Brigatinib:

Brigatinib is a substrate of the efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Given that brigatinib exhibits high solubility and high permeability *in vitro*, P-gp and BCRP inhibitors are unlikely to increase plasma concentrations of brigatinib.

Effect of Other Transporters on Brigatinib:

Brigatinib is not a substrate of organic anion transporting polypeptide (OATP1B1, OATP1B3), organic anion transporter (OAT1, OAT3), organic cation transporter (OCT1, OCT2), multidrug and toxin extrusion protein (MATE1, MATE2K), or bile salt export pump (BSEP).

Effect of Brigatinib on Transporters:

Brigatinib is an inhibitor of P-gp, BCRP, OCT1, MATE1, and MATE2K *in vitro*. Therefore, brigatinib may have the potential to increase concentrations of coadministered substrates of these transporters. Brigatinib at clinically relevant concentrations did not inhibit OATP1B1, OATP1B3, OAT1, OAT3, OCT2 or BSEP.

12 NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with brigatinib.

Treatment with brigatinib resulted in chromosomal damage in an *in vivo* mammalian erythrocyte micronucleus in the rat, but was not mutagenic in the Ames or *in vitro* mammalian chromosome aberration tests.

Dedicated animal fertility studies were not conducted with brigatinib. Testicular toxicity was observed in repeat-dose animal studies at doses resulting in exposure as low as 0.2 times the exposure in patients at the 180 mg dose. In rats, findings included lower weight of testes, seminal vesicles and prostate gland, and testicular tubular degeneration;

these effects were not reversible during the 2-month recovery period. In monkeys, findings included reduced size of testes along with microscopic evidence of hypospermatogenesis; these effects were reversible during the recovery period.

13 CLINICAL STUDIES

TKI-naïve Advanced ALK-positive NSCLC (ALTA 1L Study)

The efficacy of ALUNBRIG was demonstrated in a randomized (1:1), open-label, multicenter trial (ALTA 1L, NCT02737501) in adult patients with advanced ALK-positive NSCLC who had not previously received an ALK-targeted therapy. The study required patients to have an ALK rearrangement based on a local standard of care testing. Eligible patients were allowed to have up to 1 prior regimen of chemotherapy in the locally advanced or metastatic setting and were required to have an ECOG Performance Status of 0-2. Neurologically stable patients with treated or untreated central nervous system (CNS) metastases, including leptomeningeal metastases, were eligible. Patients with a history of interstitial lung disease, drug-related pneumonitis, or radiation pneumonitis were excluded. The major efficacy outcome measure was progression-free survival (PFS) as evaluated by a Blinded Independent Review Committee (BIRC) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Additional efficacy outcome measures as evaluated by the BIRC include confirmed overall response rate (ORR), duration of response (DOR), intracranial ORR, and intracranial DOR.

A total of 275 patients were randomized to receive ALUNBRIG 180 mg orally once daily with a 7-day lead-in at 90 mg once daily (n=137) or crizotinib 250 mg orally twice daily (n=138). Of the 275 enrolled patients, 239 had positive results using the companion diagnostic test, the Vysis ALK Break Apart FISH Probe Kit; central results were negative for 20 patients and unavailable for 16 patients.

Randomization was stratified by CNS metastases (present vs absent) and prior chemotherapy use for locally advanced or metastatic disease (yes, no).

Baseline demographic characteristics of the overall study population were: median age 59 years (range: 27 -to 89, 32% 65 and over), 59% White and 39% Asian, 55% female, 39% ECOG PS 0 and 56% ECOG PS 1, and 58% never smokers. The disease characteristics of the overall study population were: 93% with Stage IV disease; 27% received chemotherapy in the locally advanced or metastatic setting; 14% had received CNS radiation; 31% had bone metastases; and 20% had liver metastases. CNS metastases were present in 35% (n=96) of patients; 41 of those patients had measurable CNS lesions.

ALTA 1L demonstrated a statistically significant improvement in PFS by BIRC. Efficacy results from this study are described in Table 7 and Figure 1.

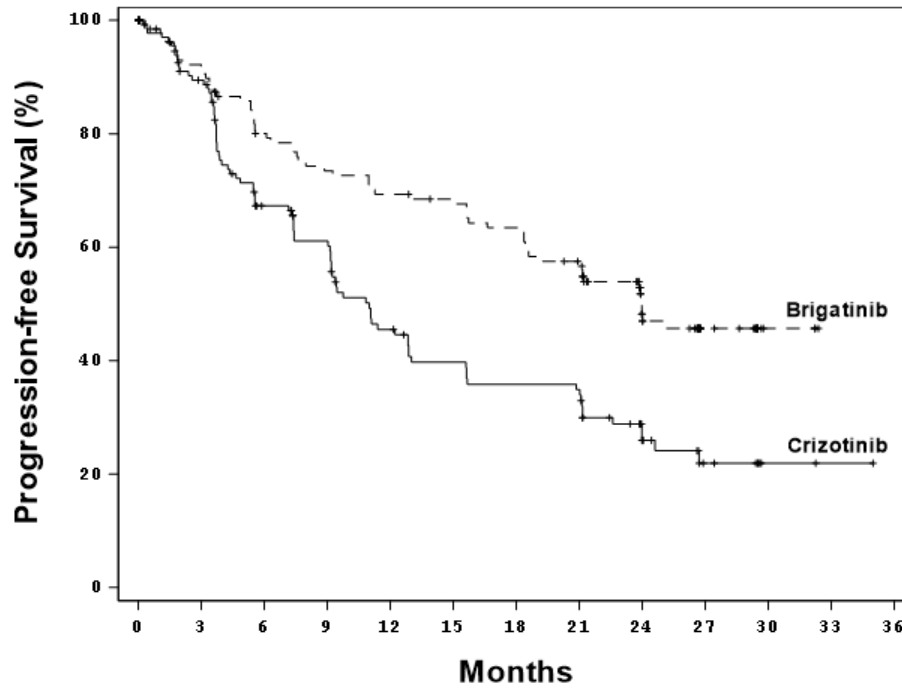
At the data cutoff point overall survival data was not mature.

Table 7: Efficacy Results by BIRC Assessment in ALTA 1L		
Efficacy Parameters	ALUNBRIG N = 137	Crizotinib N = 138
Progression-Free Survival		
Number of Events, n (%)	63 (46%)	87 (63%)
Median (months) (95% CI)	24.0 (18.5, NE)	11.0 (9.2, 12.9)
Hazard ratio (95% CI)	0.49 (0.35, 0.68)	
p-value*	<.0001	
Tumor Responses		
Confirmed Overall Response Rate, % (95% CI)	74% (66, 81)	62% (53, 70)
p-value*	0.0342	
Complete Response, % (95% CI)	15% (9, 22)	9% (5, 15)
Partial Response, % (95% CI)	59% (50, 67)	53% (44, 61)
Duration of Response		
Number of Confirmed responders	n = 101	n = 85
Median (months) (95% CI)	NR (19.4, NE)	13.8 (9.3, 20.8)
Response duration \geq 24 months	51%	30%

CI = Confidence Interval, NR=Not Reached, NE=Not Estimable

* 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

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

BIRC assessment of confirmed intracranial ORR and intracranial DOR according to RECIST v1.1 in the subgroup of 41 patients with measurable CNS metastases (≥ 10 mm in longest diameter) at baseline are summarized in Table 8. Duration of intracranial response was measured from date of first intracranial response until intracranial disease progression (new lesions, intracranial target lesion diameter growth $\geq 20\%$ from nadir, or unequivocal progression of intracranial nontarget lesions) or death.

Table 8: Intracranial Overall Response in Patients with Measurable CNS Metastases in ALTA 1L		
Efficacy Parameter	ALUNBRIG (N = 18)	Crizotinib (N = 23)
Confirmed Intracranial Overall Response Rate, (95% CI)	78% (52, 94)	26% (10, 48)
Complete Response, % (95% CI)	28% (10, 53)	0 (0, 15)
Partial Response, % (95% CI)	50% (26, 74)	26% (10, 48)
Duration of Intracranial Response		
Number of Confirmed Responders	n = 14	n = 6
Intracranial Response Duration ≥ 24 months	64%	NE

CI = Confidence Interval; NE = Not Estimable

ALK-positive Advanced or Metastatic NSCLC Previously Treated with Crizotinib

The efficacy of ALUNBRIG was demonstrated in a two-arm, open-label, multicenter trial (ALTA, NCT02094573) in adult patients with locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC) who had progressed on crizotinib. The study required patients to have a documented ALK rearrangement based on an FDA-approved test or a different test with adequate archival tissue to confirm ALK arrangement by the Vysis[®] ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit test. Key eligibility criteria included an ECOG Performance Status of 0-2 and progression on crizotinib. Neurologically stable patients with central nervous system (CNS) metastases were permitted to enroll. Patients with a history of interstitial lung disease or drug-related pneumonitis or who had received crizotinib within 3 days of the first dose of brigatinib were excluded. The major efficacy outcome measure was confirmed overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by an Independent Review Committee (IRC). Additional efficacy outcome measures included Investigator-assessed ORR, duration of response (DOR), intracranial ORR, and intracranial DOR.

A total of 222 patients were randomized to receive ALUNBRIG either 90 mg once daily (90 mg arm; n=112) or 180 mg once daily following a 7-day lead-in at 90 mg once daily (90→180 mg arm; n=110). Randomization was stratified by CNS metastases (present versus absent) and best prior response to crizotinib (complete or partial response versus any other response/unevaluable).

Baseline demographic characteristics of the overall study population were: median age 54 years (range 18 to 82, 23% 65 and over), 67% White and 31% Asian, 57% female, 36% ECOG PS 0 and 57% ECOG PS 1, and 95% never or former smokers. The disease characteristics of the overall study population were: Stage IV disease in 98%, adenocarcinoma histology in 97%, prior systemic chemotherapy in 74%, CNS metastases in 69% (61% had received prior CNS radiation), bone metastases in 39%, and liver metastases in 26% of patients. Sixty-four percent of patients had an objective response to prior crizotinib.

The median duration of follow-up was 8 months (range: 0.1-to 20.2). Efficacy results from ALTA are summarized in [Table 9](#).

Efficacy Parameter	IRC Assessment		Investigator Assessment	
	90 mg once daily (N=112)	90→180 mg once daily (N=110)	90 mg once daily (N=112)	90→180 mg once daily (N=110)
Overall Response Rate (95% CI)	48% (39,58)	53% (43,62)	45% (35,54)	54% (44,63)
Complete Response, n (%)	4 (3.6%)	5 (4.5%)	1 (0.9%)	4 (3.6%)
Partial Response, n (%)	50 (45%)	53 (48%)	49 (44%)	55 (50%)
Duration of Response, median in months (95% CI)	13.8 (7.4,NE)	13.8 (9.3,NE)	13.8 (5.6,13.8)	11.1 (9.2,13.8)

CI = Confidence Interval; NE = Not Estimable

IRC assessment of intracranial ORR and intracranial DOR according to RECIST v1.1 in the subgroup of 44 patients with measurable CNS metastases (≥ 10 mm in longest diameter) at baseline are summarized in [Table 10](#). Duration of intracranial response was measured from date of first intracranial response until intracranial disease progression (new lesions, intracranial target lesion diameter growth $\geq 20\%$ from nadir, or unequivocal progression of intracranial non-target lesions) or death.

Table 10: Intracranial Objective Response in Patients with Measurable CNS Metastases in ALTA		
Efficacy Parameter	IRC Assessment	
	90 mg once daily (N=26)	90→180 mg once daily (N=18)
Intracranial Overall Response Rate, (95 % CI)	42% (23,63)	67% (41,87)
Complete Response, n (%)	2 (7.7%)	0
Partial Response, n (%)	9 (35%)	12 (67%)
Duration of Intracranial Response		
Number of Responders	11	12
Intracranial Response Duration ≥6 months	7 (64%)	6 (50%)
Intracranial Response Duration ≥12 months	4 (36%)	3 (25%)

CI = Confidence Interval

14 SHELF LIFE

The expiry date of the product is indicated on the packaging materials.

Shelf life after first opening: 60 days or expiry date whichever comes first.

15 HOW SUPPLIED/STORAGE AND HANDLING

30 mg tablets: round, white to off-white film-coated tablets with “U3” debossed on one side and plain on the other side; available in bottles of 30 tablets.

90 mg tablets: oval, white to off-white film-coated tablets with “U7” debossed on one side and plain on the other side; available in bottles of 7 and 30 tablets.

Not all packages may be marketed.

Do not store above 30°C.

The bottle contains one sealed canister containing a molecular sieve desiccant. Keep the desiccant canister in the bottle.

16 MARKETING AUTHORISATION HOLDER

Takeda Israel Ltd.,
25 Efal st.,
P.O.B. 4140,
Petach Tikva 4951125.

17 MANUFACTURER

ARIAD Pharmaceuticals, Inc.,
40 Landsdowne Street,
Cambridge MA, U.S.A.

18 MARKETING AUTHORISATION NUMBER(S)

161-05-35334, 161-06-35335

This leaflet has been revised in October 2021 according to MoH guidelines.