Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Brigatinib

Proprietary Product Name: Alunbrig

Sponsor: Takeda Pharmaceuticals Australia Ltd

March 2020

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
90 → 180 mg	90 mg once daily lead in for 7 days, then 180 mg once daily thereafter (the proposed dosing for brigatinib)
ACM	Advisory Committee on Medicines
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALK+	Anaplastic lymphoma kinase gene rearrangement positive
ALT	Alanine aminotransferase
ARTG	Australian Register of Therapeutic Goods
ASA	Australian specific Annex
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero extrapolated to infinity
CHMP	Committee for Medicinal Products for Human Use (EU)
CI	Confidence interval
CMI	Consumer Medicines Information
CNS	Central nervous system
CPK	Creatinine phosphokinase
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCR	Disease control rate (response is at least stable disease or better)
DOR	Duration of response
EMA	European Medicines Agency (EU)
EML4	Echinoderm microtubule-associated protein-like 4
EOPE	Early onset pulmonary events

Abbreviation	Meaning
EORTC QLQ-C30 v3.0	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire version 3
EU	European Union
EU-RMP	European Union-risk management plan
FDA	Food and Drug Administration (US)
FISH	Fluorescence in situ hybridisation
ICH	International Conference on Harmonisation
IGF-1R	Insulin-like growth factor 1 receptor
IRC	Independent review committee
ITT	Intent to treat
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PAC	Patient Alert Card
PASS	Post authorisation safety studies
PD	Pharmacodynamic(s)
PFS	Progression free survival
PK	Pharmacokinetic(s)
Pop PK	Population pharmacokinetic(s)
PR	Partial response
PSUR	Periodic safety update report
QD	Once daily (Latin: *quaque die)*
RECIST	Response evaluation criteria in solid tumours
RMP	Risk management plan
ROS1	c-ros oncogene 1
SAE	Serious adverse event

Abbreviation	Meaning
SmPC	Summary of Product Characteristics (EU)
TGA	Therapeutic Goods Administration
TKI	Tyrosine kinase inhibitor
ULN	Upper limit of normal
US(A)	United States (of America)

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	4 March 2019
Date of entry onto ARTG:	6 March 2019
ARTG number:	299962, 299963, 299964, 299965, 299966, 299967, 299968
, *Black Triangle Scheme*	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
Active ingredient:	Brigatinib
Product name:	Alunbrig
Sponsor's name and address:	Takeda Pharmaceuticals Australia Pty Ltd Level 5, Chifley Tower, 2 Chifley square Sydney NSW
Dose form:	Film coated tablets
Strengths:	30, 90 and 180 mg
Containers:	Bottle, blister pack
Pack sizes:	7, 21 or 28 tablets in blister pack; 7 or 30 tablets in bottle
Approved therapeutic use:	*Alunbrig is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib.* *The approval of this medicine is based on objective response rate and duration of response in a non-comparative study.*
Route of administration:	Oral
Dosage:	ALK-positive NSCLC status should be known prior to initiation of Alunbrig therapy. A validated ALK assay is necessary for the selection of ALK-positive NSCLC patients. Treatment with Alunbrig should be initiated and supervised by a physician experienced in the use of anticancer medicinal products. The recommended starting dose of Alunbrig is 90 mg once daily for the first 7 days, then 180 mg once daily. Treatment should continue as long as clinical benefit is observed. For further information see the Product Information.

Product background

This AusPAR describes the application by Takeda Pharmaceuticals Australia Pty Ltd (the sponsor) to register Alunbrig (brigatinib) film coated tablets for the following proposed indication:

> *Alunbrig is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib*.

Most lung cancer is diagnosed at advanced stages with the majority of patients being diagnosed with regional or distant disease. Historically, lung cancers were treated according to histology (that is, small cell or non-small cell histologies, and histological subtypes such as adenocarcinoma or squamous). More recently, treatments have been developed to target underlying molecular alterations as it has become clear that histologically identical tumours will respond differently when influenced by different oncogenes.

Anaplastic lymphoma kinase (ALK) is a protein tyrosine kinase primarily involved in developmental processes, and is normally expressed at low levels in adults.[1] Several genetic rearrangements of the *ALK* gene have been identified in non-small cell lung cancer (NSCLC). In some rearrangements, such as the fusion with echinoderm microtubule-associated protein-like 4 (*EML4*) gene, the resulting hybrid protein is ligand independent and the ALK kinase domain is activated. This results in activation of multiple signalling pathways which may drive cell proliferation, survival and metastasis.[2] Activating gene rearrangements in *ALK* have been identified as driver mutations in approximately 2% to 7% of patients with NSCLC.[3,4] Inhibition of the ALK tyrosine kinase domain is effective in disrupting the signalling pathways in ALK positive (ALK+) NSCLC tumours.

At the time the submission discussed in this AusPAR was under consideration, three ALK inhibitors were registered in Australia: crizotinib (Xalkori) was the first, followed by ceritinib (Zykadia) and alectinib (Alecensa). Treatment with an ALK inhibitor is recommended in clinical practice guidelines as first line therapy for patients with ALK+ advanced NSCLC. Despite offering substantial benefits for patients with ALK+ NSCLC, use of these targeted therapies can be limited by treatment resistance and safety issues. Inadequate central nervous system (CNS) penetration can also be a factor limiting the efficacy in patients with brain metastases. Treatment is generally continued until there is evidence of disease progression or unacceptable toxicity. Patients who develop treatment resistance may benefit from switching to an alternative ALK inhibitor.

Brigatinib is an orally bioavailable, small molecule, selective ALK inhibitor, that is capable of overcoming mechanisms associated with resistance to other ALK inhibitors. Brigatinib has been reported to have action against multiple ALK variants including those most commonly associated with clinical resistance to crizotinib (L1196M and G1296A mutations);[5] and the only mutation known (to date) to be associated with clinical resistance to all three approved ALK inhibitors (G1202R mutation).[6]

[1] Camidge, D.R. and Doebele, R.C. (2012). Treating ALK-positive lung cancer--early successes and future challenges. *Nat Rev Clin Oncol*. 2012; 9: 268-277.
[2] Hallberg, B. and Palmer, R.H. (2016). The role of the ALK receptor in cancer biology. *Ann Oncol*. 2016; 27 Suppl 3:iii4-iii15.
[3] Kwak, E.L. et al. (2010). Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med*. 2010; 363: 1693-1703.
[4] Wong, D.W. et al. (2009). The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. Cancer. 2009;115(8):1723-33.
[5] Katayama, R., Lovly, C.M., and Shaw, A.T. (2015). Therapeutic targeting of anaplastic lymphoma kinase in lung cancer: a paradigm for precision cancer medicine. *Clin Cancer Res*. 2015; 21: 2227-2235.
[6] Fontana, D. et al (2015). Activity of second-generation ALK inhibitors against crizotinib-resistant mutants in an NPM-ALK model compared to EML4-ALK. *Cancer Med*. 2015; 4: 953-965.

Regulatory status

Alunbrig (brigatinib) is a new chemical entity for Australian regulatory purposes.

Brigatinib was granted orphan drug designation on 28 July 2017 for the treatment of patients with ALK positive (ALK+) non-small cell lung cancer (NSCLC).

At the time the TGA considered this application, a similar application had been approved the United States of America (USA), European Union (EU) and Canada (indications as below).

USA: Brigatinib was granted US Food and Drug Administration (FDA) accelerated approval on 28 April 2017 for the following indication:

> *Alunbrig is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. This indication is approved under accelerated approval based on tumour response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.*

EU: Marketing authorisation was granted by the European Medicine Agency (EMA) on 22 November 2018 for the following indication:

> *Alunbrig is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib.*

Canada: Brigatinib was approved with a Notice of Compliance with Conditions (NOC/c) on 27 July 2018 for the following indication:

> *Alunbrig (brigatinib) is indicated as a monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic non–small cell lung cancer (NSCLC) who have progressed on or who were intolerant to an ALK inhibitor (crizotinib).*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

Table 1 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 1: Timeline for Submission PM-2018-00586-1-4

Description	Date
Designation (Orphan)	28 July 2017
Submission dossier accepted and first round evaluation commenced	4 April 2018
First round evaluation completed	3 September 2018

Description	Date
Sponsor provides responses on questions raised in first round evaluation	30 October 2018
Second round evaluation completed	21 December 2018
Delegate's Overall benefit-risk assessment	21 December 2018
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	4 March 2019
Completion of administrative activities and registration on the ARTG	6 March 2019
Number of working days from submission dossier acceptance to registration decision*	190

*Statutory timeframe for standard applications is 255 working days

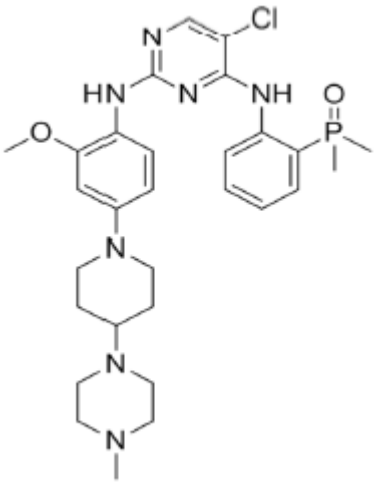
III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

Brigatinib is a small molecule potent tyrosine kinase inhibitor (TKI) and second generation ALK inhibitor, structure shown in Figure 1. Brigatinib targets tyrosine kinases ALK, c-ros oncogene 1 (ROS1), and insulin-like growth factor 1 receptor (IGF-1R). Among these, brigatinib is most active against ALK.

Figure 1: Structure of brigatinib



The chemistry evaluator has assessed the application and supporting data relating to the composition, development, manufacture, quality control and stability of brigatinib. The issues raised have been resolved.

The PI and labels are acceptable from a quality perspective.

Nonclinical

The following points were summarised from the nonclinical evaluation:

- The submitted nonclinical dossier was in accordance with the International Conference on Harmonisation (ICH) guideline for the nonclinical assessment of anticancer pharmaceuticals (ICH S9).[7]
- The primary pharmacology studies demonstrated the ALK inhibitory activity of brigatinib against ALK+ tumours at clinically achievable concentrations.
- The pharmacokinetic (PK) profile in animals was qualitatively similar to that of humans.
- The main targets for toxicity in the animal studies at exposures achieved clinically include the kidneys, heart, liver, gastrointestinal tract, haematopoietic and lymphoid organs, pancreas and testes. Safety pharmacology and toxicity studies indicate brigatinib may exert cardiovascular effects in patients, including bradycardia and hypertension. Brigatinib is not predicted to prolong the QT interval in patients.[8]
- The nonclinical studies predict embryofetal toxicity if administered to pregnant patients at the proposed clinical dose. The sponsor has proposed Australian Pregnancy Category D;[9] which is considered appropriate.
- The evaluator had no objection to the registration of brigatinib for the proposed indication provided key safety concerns are adequately addressed in the risk management plan (RMP). The evaluator also recommended changes to the PI.

Clinical

The clinical dossier contained the following:

- Bioequivalence studies comparing 30 mg, 90 mg and 180 mg tablets.
- Validation reports for methods of identifying brigatinib in human plasma and urine.
- A report of protein binding of brigatinib in human plasma.
- Healthy subject pharmacokinetics and tolerability reports.
- Evaluation of pharmacokinetics and safety of brigatinib in patients with chronic hepatic impairment and chronic renal impairment.
- Intrinsic and extrinsic factor pharmacokinetic (PK) study reports.
- Pharmacokinetics associated with co-administration with other drugs or with food.

[7] European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Note For Guidance On Nonclinical Evaluation For Anticancer Pharmaceuticals, EMEA/CHMP/ICH/646107/2008, December 2008.
[8] The QT interval is the time taken from the start of the QRS wave complex to the end of the corresponding T wave on an electrocardiograph and approximates from the start of cardiac ventricular contraction to the end of cardiac ventricular relaxation. The QTc is the QT interval corrected for heart rate.
[9] Australian Pregnancy Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

- Population PK study report.
- Clinical study reports (and associated documents) for Studies AP26113-11-101 and AP26113-13-201 (also known as the ALTA trial).
- Protocols for Studies AP26113-16-901 and AP2611313-301.
- Integrated summaries of efficacy and safety, a pulmonary adverse event review, and a modelled predication of systemic exposure to brigatinib in cytochrome p450 (CYP) enzyme 3A4 mediated drug interactions.

There are two studies addressing the efficacy of brigatinib in patients with ALK rearrangements who are resistant to crizotinib.

The pivotal study for the submission is a Phase II study of brigatinib in patients with ALK+ NSCLC who have been previously treated with crizotinib (Study AP26113-13-201). The study randomised patients to two different dosing regimens of brigatinib (90 mg once daily (QD) versus 180 mg QD with a 7 day lead-in at 90mg QD (90 → 180 mg QD). The primary outcome was objective response rate (ORR). Secondary efficacy outcomes included disease control rate, time to/duration of response, progression-free survival (PFS), overall survival and time on treatment. Other secondary outcomes included safety and tolerability of brigatinib, the measurement of steady-state plasma levels of brigatinib and health related quality of life. Exploratory outcomes were correlation of brigatinib exposure with both efficacy and safety and correlation of biomarkers with efficacy and safety. A pre-specified subgroup analysis assessed CNS response and PFS in patients with active brain metastases.

As supporting evidence, the dossier also contains a Phase I/II open label study (Study AP26113-11-101) that reported on 137 patients enrolled in either a dose escalation cohort (n = 66) or one of 5 expansion cohorts (n = 71). Patients in the dose escalation cohort could have any malignancy, however, only 9 patients across the entire study had diagnoses other than NSCLC. A total of 79 patients were enrolled with ALK+ NSCLC, of which 71 had prior exposure to crizotinib.

Pharmacology

Pharmacokinetics

The clinical PK of brigatinib were assessed in healthy subjects and cancer patients, with much of the pharmacokinetics derived from Study AP26113-11-101 which included patients with advanced malignancies, including ALK+ NSCLC.

Bioequivalence of the 30 mg, 90 mg and 180 mg tablets was confirmed in two bioequivalence studies in healthy subjects. Brigatinib exhibits linear PK in the dose range of 60 mg to 240 mg.

Administration with food had minimal impact on the pharmacokinetics of brigatinib. In the pivotal food-effect study, peak plasma levels were reduced by 13% with no effect on area under the plasma concentration-time curve (AUC) in healthy subjects administered brigatinib after a high-fat meal compared to overnight fasting. The food studies support the guidance that brigatinib may be taken with or without food.

CYP2C8 and CYP3A4 appear to be the major cytochrome P450 (CYP) isozymes responsible for brigatinib metabolism, with minor contribution from CYP3A5. Due to large effects on brigatinib exposure, co-administration with either strong CYP3A inducers or inhibitors should be avoided. No dose adjustment is required during co-administration with strong CYP2C8 inhibitors.

Brigatinib is primarily eliminated (either unchanged or as metabolite AP26123) in faeces (hepatic elimination), with a smaller proportion excreted in urine.

The PK of brigatinib in hepatic impairment was assessed in Study AP26113-15-107, a single dose study, consistent with the TGA adopted EMA guidelines.[10] Based on the findings of this study, no change in dosing is proposed for patients with Child-Pugh A or Child-Pugh B hepatic impairment, but a starting dose of 60 mg daily for the first 7 days (instead of 90 mg daily), increasing to 120 mg daily (instead of 180 mg daily) is proposed for patients with Child-Pugh C hepatic impairment.[11] This dose adjustment is based on the 37% area under the plasma concentration-time curve from time zero extrapolated to infinity ($AUC_{0-\infty}$) increase in unbound brigatinib in 6 patients with Child-Pugh C hepatic impairment exposed to a single 90 mg dose of brigatinib, compared to 9 healthy matched subjects. A warning has been added to the PI that the safety of brigatinib in patients with hepatic impairment has not been studied (patients with hepatic impairment were excluded from Study AP26113-11-101 and Study AP26113-13-201).

No dose reductions are proposed for patients with mild to moderate renal impairment. The population pharmacokinetics (pop PK)analyses suggest that brigatinib clearance is not substantially different in patients with mild and moderate renal impairment. Dose reduction is proposed for patients with severe renal impairment based on extrapolation from the PK-based study, as no patients with severe renal impairment were included in the clinical studies. A warning has been added to the PI that the safety of brigatinib in patients with severe renal impairment has not been studied.

Population pharmacokinetics data

Pop PK analyses included data from 443 subjects in five brigatinib studies: Study AP26113-11-101 (in patients with advanced malignancies including ALK+ NSCLC), Study AP26113-13-102 (in healthy subjects), Study AP26113-13-103 (food effect study in healthy subjects), Study AP26113-15-105 (drug-drug interaction study in healthy subjects) and Study AP26113-13-201 (pivotal Phase II study in ALK+ NSCLC patients post-crizotinib therapy). The TGA pop PK Working Group reviewed the findings of the US Food and Drug Administration (FDA) analysis of the pop PK model and advised that the modelling was robust and that further independent replication was not necessary. The TGA Working Group agreed with the FDA assessment.

None of the covariates (body weight, gender, race, age, alanine transferase, albumin, creatinine clearance) had a clinically meaningful influence on brigatinib PK.

The pop PK Working Group supports the proposed posology, but recommends inclusion of a warning in the PI about co-administration of drugs with narrow therapeutic indices which are substrates for either P-glycoprotein or breast cancer resistance protein (BCRP).

Pharmacodynamics

The pharmacodynamics (PD) of brigatinib are based largely on *in vitro* studies. In Study AP26113-13-201, there was a trend to increasing ORR with increasing exposure over the first 3 quartiles but this did not continue in the fourth quartile. Based on small numbers, intracranial response appeared to improve with increasing exposure to brigatinib. Adverse events (AEs) and safety related outcomes were not significantly related to increasing brigatinib exposure.

[10] EMA, Committee for Medicinal Products for Human Use (CHMP), Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function, CPMP/EWP/2339/02, February 2005.

[11] The Child-Pugh score is a system for assessing the prognosis for chronic liver disease and is based on 5 clinical measures. Class A: 5 to 6 points, least severe liver disease, one to five year survival rate of 95%. Class B: 7 to 9 points, moderately severe liver disease, one to five year survival of 75%. Class C: 10 to 15 points, most severe liver disease, 1 to 5 year survival rate 50%.

Dose finding

Study AP26113-11-101 determined 180 mg daily as being the recommended Phase II dose, but cases of early onset pulmonary events were identified during clinical development so Study AP26113-13-201 randomised patients into a 90 mg daily arm and a 180 mg daily arm (after a 7 day 90 mg daily lead in).

Efficacy

Study AP26113-11-201 (ALTA trial)

Study AP26113-11-201 (the ALTA trial), the pivotal study for this submission, was a Phase II, non-comparative, two-arm, randomised, open label, multicentre study of brigatinib in patients with ALK+ NSCLC who previously progressed on crizotinib. Patients were randomised in a 1:1 ratio to receive one of two dose regimens of brigatinib, either 90 mg daily (Arm A) or 90 mg daily for 7 days followed by 180 mg daily (Arm B). The study was not designed to compare the two arms statistically.

The inclusion and exclusion criteria were appropriate and consistent with the proposed target population. Patients had histologically/cytologically confirmed locally advanced or metastatic ALK+ NSCLC with progressive disease while on crizotinib. ALK rearrangement was determined by Vysis ALK Break-Apart fluorescence *in situ* hybridisation (FISH) Probe Kit or by a different test with adequate archival tissue available for the Vysis FISH test.

222 patients were enrolled in the study between June 2014 and September 2015, with 112 patients randomised to Arm A and 110 patients to Arm B. Randomisation was stratified by brain metastases (present versus absent) and response to prior crizotinib (complete response or partial response versus other or unknown). The data cut-off date for the clinical study report was 31 May 2016, with an additional data update report provided through to 21 February 2017.

217 patients (97.7%) had Stage IV disease at Baseline. Only 5 patients (2.3%), 3 in Arm A and 2 in Arm B, had Stage III disease at Baseline. 154 patients (69.4%) had brain metastases at Baseline.

The primary endpoint was confirmed ORR as per investigator-assessed Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[12] ORR was defined as the proportion of patients who have confirmed complete response (CR) or partial response (PR; confirmed ≥ 4 weeks after initial response) in the intent to treat (ITT) population. Independent review committee (IRC)-assessed confirmed objective response rate per RECIST v1.1 was a secondary endpoint. Other secondary endpoints included CNS response (ORR and PFS), time to response, duration of response (DOR), time on treatment, disease control rate (DCR), PFS, overall survival (OS) and patient reported symptoms (European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire version 3 (EORTC QLQ-C30 v3.0)).

The primary outcome, confirmed ORR assessed by investigators per RECIST v1.1, was 55.5% in Arm B and 45.5% in Arm A (Table 2). Independent review committee-assessed objective response rates were 54.5% in Arm B and 50.9% in Arm A. The estimated median duration of response in Arm B was 13.8 months (Table 3). Duration of response was similar when measured in patients with IRC assessed confirmed response.

[12] Eisenhauer, E.A. et al. et al (2009). New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) *Eur J Cancer*, 2009, 45: 228-247

Table 2: Investigator-assessed (primary outcome) and independent review committee-assessed confirmed objective response rates (intent to treat population), data cut off 21 February 2017

		Investigator-assessed		Independent review committee-assessed	
		Arm A 90mg daily (N = 112)	**Arm B** 90 - 180 mg daily (N = 110)	**Arm A** 90 mg daily (N = 112)	**Arm B** 90 - 180 mg daily (N = 110)
Confirmed ORR, n (%)		51 (45.5)	61 (55.5)	57 (50.9)	60 (54.5)
97.5% CI	95% CI[a]	(34.8-56.5)	(44.3-66.2)	(41.3-60.5)	(44.8-64.1)
Complete Response, n (%)		2 (1.8)	5 (4.5)	6 (5.4)	6 (5.5)
Partial Response, n (%)		49 (43.8)	56 (50.9)	51 (45.5)	54 (49.1)

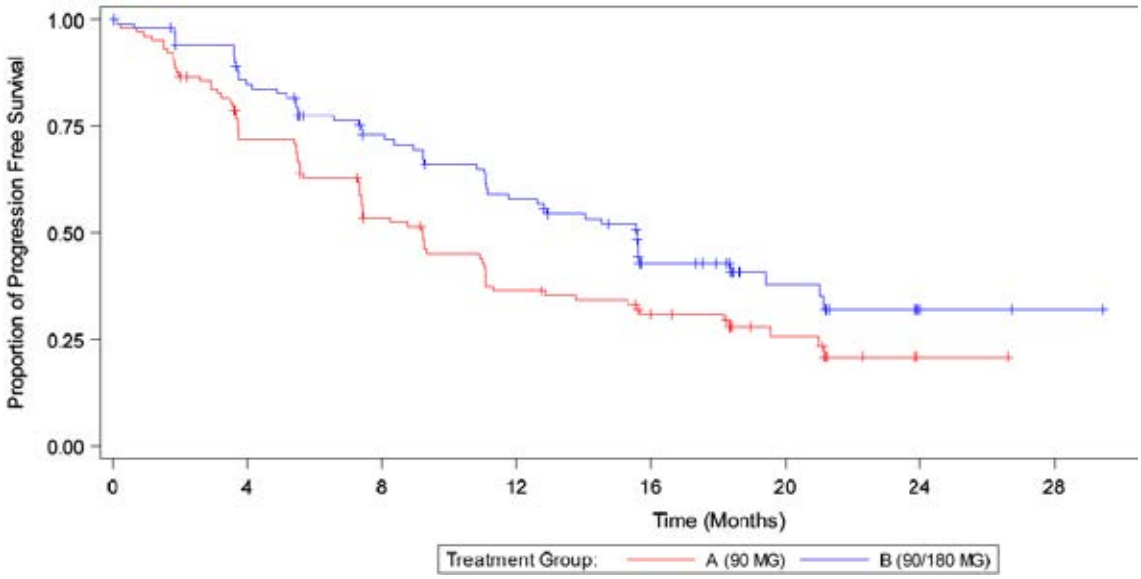
a: A 97.5% confidence interval is used for investigator assessed ORR and a 95% confidence is used for Independent review committee assessed ORR. CI = confidence interval.

Table 3: Kaplan Meier estimates of duration of response in patients with an investigator-assessed confirmed response (data cut off 21 February 2017)

	Arm A (90 mg) N = 51	Arm B (90/180 mg) N = 61	Total N = 112
Median months (95% CI)	12.0 (9.2, 17.7)	13.8 (10.2, 17.5)	13.7 (9.9, 14.8)
6 month (95% CI)	71.4% (56.6, 82.0)	84.4% (72.2, 91.6)	78.4% (69.3, 85.1)
12 month (95% CI)	52.1% (37.1, 65.1)	58.5% (44.3, 70.2)	55.5% (45.4, 64.5)

Investigator-assessed median progression free survival was 15.6 months (95% CI 11.1 to 19.4) in Arm B (90 mg to 180 mg daily) and 9.2 months (95% CI 7.4 to 11.1) in Arm A (90 mg daily), with the hazard ratio between the arms being 0.64 (95% CI 0.45 to 0.91). The apparent dose-response for median PFS provides support for the proposed dosage regimen (Figure 2). Findings for OS were not sufficiently mature to interpret, particularly in the setting of a non-comparative study.

Figure 2: Kaplan-Meier plot of investigator-assessed progression free survival by treatment arm in the intention to treat population (data cut-off 21 February 2017)



Updated data from Study AP26113-11-201 through to 29 September 2017 were provided and are consistent with the data described above. For the 90 mg to 180 mg daily arm, confirmed the ORR was 56.4% (97.5% CI 45.2 to 67.0), median duration of response was 13.8 months and median PFS was 15.6 months (95% CI 11.1 to 21.0).

Intracranial ORR for patients with measurable brain metastases at Baseline was 66.7% in Arm B and 50.0% in Arm A (Table 3). In patients with any brain metastases at Baseline, 53.4% in Arm A and 65.6% in Arm B had a response of 12 months or greater. Median CNS PFS was 12.8 months (95% CI 9.0 to 18.3) in Arm A and 18.4 months (95% CI 12.6, NA) in Arm B.

Table 4: Independent review committee assessed intracranial objective response rates by treatment arm (data cut-off 21 February 2017)

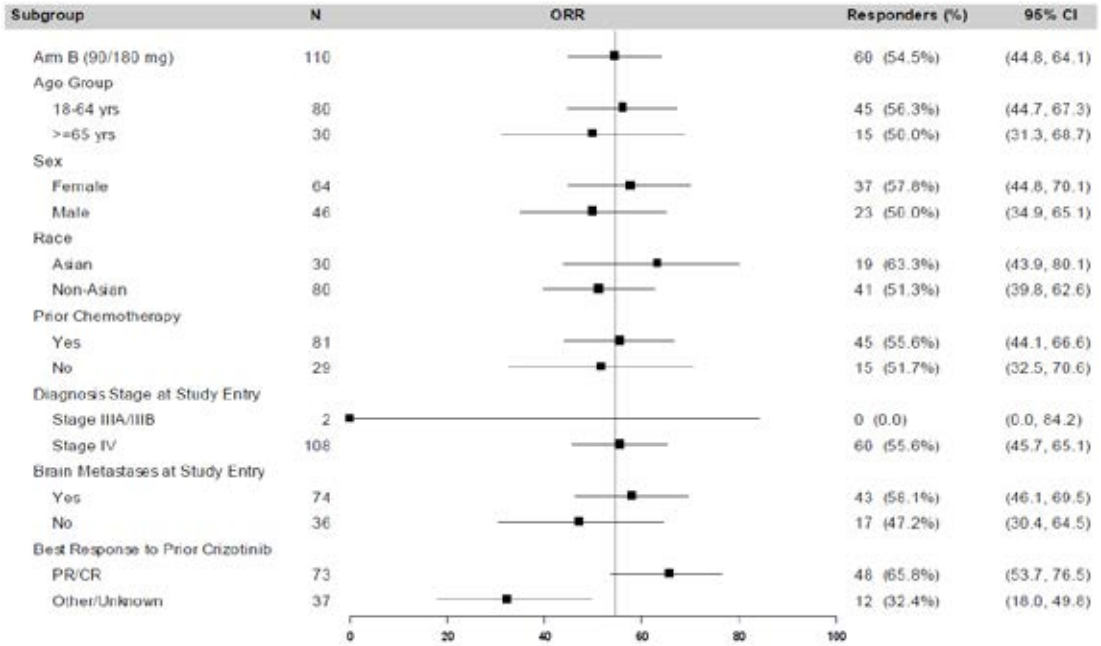
Intracranial efficacy parameter	Measurable brain metastases at Baseline			Only non-measurable brain metastases at Baseline		
	Arm A 90 mg daily (N = 26)	Arm B 90 → 180 mg daily (N = 18)	Total (N = 44)	Arm A 90 mg daily (N = 54)	Arm B 90 → 180 mg daily (N = 55)	Total (N = 109)
Confirmed intracranial ORR[a]						
n (%)	13 (50.0)	12 (66.7)	25 (56.8)	4 (7.4)	10 (18.2)	14 (12.8)
95% CI	29.9, 70.1	41.0, 86.7	41.0, 71.7	2.1, 17.9	9.1, 30.9	7.2, 20.6
Best intracranial overall response status, n (%)						
Confirmed CR	2 (7.7)	0	2 (4.5)	4 (7.4)	10 (18.2)	14 (12.8)
Confirmed PR	11 (42.3)	12 (66.7)	23 (52.3)	0	1 (1.8)	1 (0.9)

Intracranial efficacy parameter	Measurable brain metastases at Baseline			Only non-measurable brain metastases at Baseline		
	Arm A 90 mg daily (N = 26)	Arm B 90 → 180 mg daily (N = 18)	Total (N = 44)	Arm A 90 mg daily (N = 54)	Arm B 90 → 180 mg daily (N = 55)	Total (N = 109)
Intracranial disease control rate						
n (%)	22 (84.6)	15 (83.3)	37 (84.1)	40 (74.1)	48 (87.3)	88 (80.7)
95% CI	65.1. 95.6	58.6, 96.4	69.9, 93.4	60.3, 85.0	75.5, 94.7	72.1, 87.7

a: Confirmed objective response rate is defined as the proportion of patients who achieved confirmed complete response per RECIST v1.1

Outcomes for subgroup analyses of the primary efficacy outcome for Arm B are shown in Figure 3. Patients who had previously achieved a complete response or a partial response to crizotinib, were more likely to achieve an objective response to brigatinib 180 mg daily (65.8% (95% CI 53.7 to76.5%)) than those whose best response was stable disease, progression or unknown (32.4% 95% CI (18 to49.8%)). Patients in Arm B with brain metastases at study entry were numerically more likely to achieve an objective response (58.1%) compared to those without brain metastases (47.2%). In contrast, patients with brain metastases at study entry who were treated with brigatinib 90 mg daily (Arm A) were numerically less likely to achieve an objective response (38.8%) compared to those without brain metastases (59.4%).

Figure 3: Forest plot of investigator-assessed confirmed objective systemic response (Arm B: 90/180 mg daily) in the intent to treat population (data cut-off 31 May 2016)



Arm B (90/180 mg); patients were treated with 90 mg brigatinib once daily (QD) for 7 days, increased to 180 mg brigatinib QD thereafter.

The submission included matching adjusted indirect comparisons of ceritinib and alectinib studies. Further matching adjusted indirect comparisons using alternative censoring rules for PFS were provided. These comparisons suggest that brigatinib is not inferior to ceritinib and alectinib, but they do not provide robust evidence of the comparative efficacy of brigatinib.

The submission did not provide direct comparative data, other than top-line results from the first planned interim analysis of the Phase III ALTA-1L clinical trial. The interim findings from ALTA-1L trial were published in the New England Journal of Medicine on 22 November 2018:[13]

> 'A total of 275 patients underwent randomization; 137 were assigned to brigatinib and 138 to crizotinib. At the first interim analysis (99 events), the median follow-up was 11.0 months in the brigatinib group and 9.3 months in the crizotinib group. The rate of progression free survival was higher with brigatinib than with crizotinib (estimated 12 month progression free survival, 67% (95% confidence interval (CI), 56 to 75%) versus 43% (95% CI, 32 to 53%); hazard ratio for disease progression or death, 0.49 (95% CI, 0.33 to 0.74); $p < 0.001$ by the log-rank test). The confirmed objective response rate was 71% (95% CI, 62 to 78%) with brigatinib and 60% (95% CI, 51 to 68%) with crizotinib; the confirmed rate of intracranial response among patients with measurable lesions was 78% (95% CI, 52 to 94%) and 29% (95% CI, 11 to 52%), respectively. No new safety concerns were noted.'

Study AP26113-11-101

This was a Phase I/II single arm, open label, multicentre, dose finding and cohort expansion study to evaluate the safety, tolerability, pharmacokinetics and preliminary anti-tumour activity of brigatinib. The study enrolled 137 patients, of which 79 had ALK+ NSCLC (71 of these patients had received prior crizotinib). Patients were allocated to six cohorts that differed by dosing. The small numbers and different dosing cohorts limit the conclusions that can be drawn from this study regarding efficacy.

In the cohort expansion part of the study, the primary endpoint was the ORR (using RECIST v1.1);[12] except for Cohort 5, for which the primary endpoint was the intracranial response rate (using RECIST v1.1). The confirmed ORR in the 90 → 180 mg daily dose group was 76% (19 out of 25). Intracranial objective response rate was 66.7% (10 out of 15) and 41.9% (13 out of 31) in patients with measurable and non-measurable brain metastases, respectively. These results are broadly consistent with the efficacy findings in the Study AP26113-13-201 (the ALTA trial).

Safety

The evaluation of safety for this submission is based primarily on Studies AP26113-11-101 and AP26113-13-201 (the ALTA trial).

In Study AP26113-11-101, 137 patients, including 79 patients with ALK+ NSCLC, received brigatinib in dosages ranging from 30 mg to 300 mg daily (14 patients with ALK+ NSCLC received 90 mg daily and 28 received 90 → 180 mg). In Study AP26113-13-201, 219 patients with ALK+ NSCLC were treated with brigatinib; 109 received 90 mg daily and 110 received 90 → 180 mg. Median follow up for both arms of Study AP26113-13-201 was 17.9 months, with median exposure for the 90 → 180 mg daily arm of more than 17 months.

[13] Camidge, D.R. et al. (2018). Brigatinib versus Crizotinib in ALK-Positive Non–Small-Cell Lung Cancer. *N Engl J Med*, 2018; 379: 2027-2039.

In addition, the submission provided safety data for 208 healthy subjects in seven pharmacology studies who received brigatinib 90 mg, 120 mg or 180 mg. Serious adverse event (SAE) data from the ongoing Phase III Study AP26113-13-301 and from Expanded Access Programs in Europe and USA were also provided.

A summary of AEs in Studies AP26113-11-101 and AP26113-13-201 is provided in Table 5. Almost all patients receiving brigatinib experienced at least one adverse event. Patients receiving brigatinib 90 → 180 mg daily were more likely to experience AEs of Grade 3 or greater. Adverse events leading to discontinuation were higher with 90 → 180 mg daily dosing than 90 mg daily dosing.

Overall rates of SAEs were similar across the two arms of the ALTA trial, but there were higher rates of pneumonia and pneumonitis in the 90 → 180 mg daily arm compared to the 90 mg daily arm, which were offset by a higher rate of neoplasm progression in the 90 mg daily arm (Table 6). The higher rates of pneumonia and pneumonitis are notable because early onset pulmonary events (EOPE) were identified during early clinical development, leading to the two-arm design of the Phase II ALTA trial (Arm A 90 mg daily; Arm B 90 → 180 mg).

Table 5: Overview of adverse events in Study AP26113-11-101 and Study AP26113-13-201, safety population, data cut-off 31 May 2016

	Study AP26113-11-101			Study AP26113-13-201		
	ALK+ NSCLC 90 mg daily (N = 14)	ALK+ NSCLC 90 → 180 mg daily (N = 28)	All patients (N= 137)	Arm A 90 mg daily (N = 109)	Arm B 90 → 180 mg daily (N = 110)	All patients (N = 219)
Any treatment emergent AE	14 (100.0)	27 (96.4)	136 (99.3)	108 (99.1)	110 (100.0)	218 (99.5)
Treatment-related AE	13 (92.9)	27 (96.4)	126 (92.0)	85 (78.0)	101 (91.8)	186 (84.9)
Treatment emergent AE Grade ≥ 3	8 (57.1)	20 (71.4)	94 (68.6)	53 (48.6)	60 (54.5)	113 (51.6)
Treatment-related AE Grade ≥ 3	5 (35.7)	18 (64.3)	58 (42.3)	22 (20.2)	38 (34.5)	60 (27.4)
SAE	6 (42.9)	10 (35.7)	68 (49.6)	43 (39.4)	48 (43.6)	91 (41.6)
Treatment-related SAE	2 (14.3)	4 (14.3)	25 (18.2)	8 (7.3)	19 (17.3)	27 (12.3)
SAE Grade ≥ 3	6 (42.9)	9 (32.1)	60 (43.8)	31 (28.4)	37 (33.6)	68 (31.1)
Treatment-related SAE Grade ≥ 3	2 (14.3)	3 (10.7)	20 (14.6)	6 (5.5)	12 (10.9)	18 (8.2)

	Study AP26113-11-101			Study AP26113-13-201		
Treatment emergent AE leading to dose reduction, dose interruption, or dose discontinuation	6 (42.9)	17 (60.7)	75 (54.7)	43 (39.4)	59 (53.6)	102 (46.6)
Treatment emergent AE leading to dose interruption	6 (42.9)	16 (57.1)	68 (49.6)	42 (38.5)	54 (49.1)	96 (43.8)
Treatment emergent AE leading to dose reduction	0	6 (21.4)	18 (13.1)	9 (8.3)	25 (22.7)	34 (15.5)
Treatment emergent AE leading to dose discontinuation	1 (7.1)	4 (14.3)	15 (10.9)	3 (2.8)	11 (10.0)	14 (6.4)

Table 6: Treatment emergent serious adverse events (in ≥ 2% of total study population) in Study AP26113-13-201 by treatment arm (data cut-off 21 February 2017)

Preferred Term	Arm A 90 mg daily N = 109	Arm B 90 → 180 mg daily N = 110	Total N = 219
Subjects with at least 1 event, n (%)	52 (47.7)	56 (50.9)	108 (49.3)
Neoplasm progression	18 (16.5)	8 (7.3)	26 (11.9)
Pneumonia	4 (3.7)	9 (8.2)	13 (5.9)
Pneumonitis	2 (1.8)	9 (8.2)	11 (5.0)
Malignant pleural effusion	4 (3.7)	4 (3.6)	8 (3.7)

In the integrated summary of safety, deaths were more common in patients receiving 90 mg daily than 90 → 180 mg daily. The majority of deaths in both dosage groups were due to neoplasm progression. There was no signal to indicate a relationship between brigatinib treatment and death due to a particular cause; in particular, there was no signal for pulmonary-related deaths in either group.

AEs leading to discontinuations occurred in 10.9% of patients in Study AP26113-11-101 and 6.4% of patients in Study AP26113-13-201. Discontinuations were more common in patients receiving the 90 → 180 mg daily dose compared with the 90 mg daily dose, but absolute numbers are small (Table 5).

Four cases of definite early onset pulmonary events and 10 cases of possible early onset pulmonary events were identified in Study AP26113-13-201 (14 out of 219, 6.4%). All occurred at the 90 mg daily dose (that is, none were identified following escalation to 180 mg daily). Six were Grade 3 or 4, and one was Grade 5. Seven patients discontinued brigatinib and 6 had dose interruption. There was one death which was assessed by the investigator as not related to brigatinib, however the event met the definition of possible early onset pulmonary events. In Study AP26113-11-101, 6 patients had definite early onset pulmonary eventss and 5 patients had possible early onset pulmonary events (11 out of 137, 8.0%). Two early onset pulmonary events s were fatal, and all but one event was Grade 3 or higher. The risk of early onset pulmonary events appears higher in patients aged ≥ 65 years.

Treatment-emergent bradycardia adverse events occurred in 4.2% (15 out of 356) patients in Studies AP26113-11-101 and AP26113-13-201 combined, and was observed in similar proportions in the 90 mg daily and 90 → 180 mg daily dose groups. Bradycardia was considered treatment related in 2.2% (8 out of 356), but did not lead to treatment interruption, dose reduction or discontinuation.

Treatment emergent hypertension adverse events occurred in 17.4% (62 out of 356) patients across Studies AP26113-11-101 and AP26113-13-201, and occurred more commonly in the 90 → 180 mg daily dose groups (22.5%) compared with the 90 mg daily dose groups (13.8%). Grade 3 or greater hypertension events occurred in 7.2% (10 out of 138) of patients in the 90 → 180 mg daily dose groups and 4.9% (6 out of 123) of patients in the 90 mg daily dose groups. No patients discontinued due to a hypertension event.

Treatment emergent gastrointestinal adverse events occurred in 74.4% (265 out of 356) of patients across Studies AP26113-11-101 and AP26113-13-201. Grade 3 or greater events occurred in 3.9% (14 out of 356) patients overall, most commonly nausea (1.1%), diarrhoea (0.8%) and vomiting (0.6%). No patients discontinued due to gastrointestinal adverse events.

Blood creatinine phosphokinase (CPK) was increased in 39.3% (86 out of 219) of patients in Study AP26113-13-201, and occurred more frequently in the 90 → 180 mg daily dose group (49.1%) compared with the 90 mg daily dose group (29.4%). Increases to Grade 3 or 4 in patients with less than Grade 3 CPK at Baseline occurred in 11.8% of patients in the 90 → 180 mg daily dose group, and 2.8% in the 90 mg daily dose group. An important potential risk of 'Myopathy, including rhabdomyolysis and cardiomyopathy' has been included in the risk management plan (RMP) safety specification.

Treatment emergent clinical pancreatitis adverse events occurred in 2 patients in Study AP26113-11-101 (both were SAEs) and none in Study AP26113-13-201. Treatment emergent chemical pancreatitis adverse events occurred in 21.6% (77 out of 356) of patients across both studies. Events were more common in the 90 → 180 mg daily dose groups (26.8%) compared with the 90 mg daily dose groups (14.6%).

Treatment emergent vision impairment events occurred in 16.6% (59 out of 356) of patients across Studies AP26113-11-101 and AP26113-13-201, but only 4.5% were considered to be treatment related. The most common reported events were vision blurred (5.3%, 19 out of 356) and diplopia (2.2%, 8 out of 356) but none were Grade 3 or higher. One Grade 3 event (macular oedema) was assessed as treatment-related.

Insulin was evaluated because there was preclinical evidence of brigatinib inhibition of the insulin-like growth factor receptor which may lead to insulin resistance and elevated blood glucose level. Grade 3 or greater treatment emergent increased insulin or hyperglycaemia events occurred in 0.6% (2 out of 356) of patients across Studies AP26113-11-101 and AP26113-13-201. Hyperglycaemia of any grade was observed in 3.4% of patients across both studies.

Treatment emergent peripheral neuropathy occurred in 28.7% (102 out of 357) of patients across Studies AP26113-11-101 and AP26113-13-201. The rate was higher in patients in the 90 → 180 mg daily dose group (33.3%) compared with the 90 mg daily dose group (24.4%).

Increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were common, occurring in 40% and 53% of patients, respectively, in Study AP26113-13-201. Events were slightly more common in the 90 → 180 mg daily dose group than the 90 mg daily dose group. The proportion of patients moving from a baseline Common Terminology Criteria for Adverse Events (CTCAE) Grade of < 3 to CTCAE Grade 3 or greater was low. Hepatic events resulted in dose reductions in 0.6% of patients and no patients discontinued. No Hy's law cases were observed.[14]

The sponsor provided updated safety data from Study AP26113-13-201 (data cut-off 29 September 2017, median duration of exposure 522 days in Arm B) as well as new safety data from the first interim analysis of the ALTA-1L trial and reported safety data for approximately 1,156 patients treated outside of the clinical development program. The safety profile of brigatinib is largely unchanged based on these additional safety data. The ALTA-1L trial has not been fully evaluated in this submission but the interim safety data indicate fewer gastrointestinal toxicity events and SAEs compared to crizotinib but more elevated CPK and hypertension events.

Risk management plan

European Union-risk management plan (EU-RMP) version 4.1 (dated 8 December 2017; data lock point (DLP) 31 May 2016) and Australian specific Annex (ASA) version 1.0 (dated February 2018) were submitted in support of this application. EU-RMP version 4.3 (dated 19 June 2018; DLP 31 May 2016) and ASA version 2.0 (dated October 2018) were subsequently submitted.

The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 7.[15]

Table 7: Summary of safety concerns and associated risk monitoring and mitigation strategies

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Pulmonary toxicity (including early onset pulmonary events and later onset pneumonitis)	ü	ü	ü	ü*

[14] Hy's Law: Evidence of hepatocellular injury with ALT and/or AST > 3 x the upper limit of normal (ULN) and total bilirubin > 2 x ULN, and no other reason to explain rise in aminotransferases and total bilirubin.

[15] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	Hypertension	ü	–	ü	ü*
	Bradycardia	ü	–	ü	ü*
	Drug-drug interaction with strong CYP3A inhibitors and strong and moderate CYP3A inducers	ü	–	ü	–
Important potential risks	Hepatotoxicity	ü	–	ü	–
	Myopathy, including rhabdomyolysis and cardiomyopathy	ü	–	ü	–
	Pancreatitis	ü	–	ü	–
	Retinal degeneration, macular degeneration	ü	–	ü	–
	Embryofetal and developmental toxicity	ü	–	ü	–
Missing information	Effects on male and/or female fertility	ü	–	ü	–
	Long term safety	ü	ü	–	–
	Drug-drug interaction with CYP3A4 substrates	ü	–	ü	–

*Additional risk minimisation activity in the EU Only; Patient Alert Card (PAC).

EU post authorisation safety studies (PASS; incorporating the US and EU studies) is listed as additional pharmacovigilance. The objectives of EU PASS are to describe the occurrence, clinical management and outcomes of early onset pulmonary events and assess patient receipt and use of the PAC. No additional risk minimisation activities are planned in Australia.

The RMP evaluator has recommended the following conditions of registration:

- The Alunbrig (brigatinib) EU-RMP (version 4.3, dated 19 June 2018, DLP 31 May 2016), with ASA (October 2018), included with submission PM-2018-00586-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).
- Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.
- The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes.

Note that submission of a PSUR does not constitute an application to vary the registration.

- Alunbrig (brigatinib) is to be included in the Black Triangle Scheme. The PI and Consumer Medicines Information (CMI) for Alunbrig must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

Risk-benefit analysis

Delegate's considerations

Pharmacology

The PK of brigatinib in hepatic impairment was assessed in a single dose pharmacokinetic study, consistent with the TGA-adopted EMA guideline.[10] Total brigatinib exposure was reduced in patients with hepatic impairment but there was a 37% increase in unbound brigatinib in patients with Child-Pugh C hepatic impairment. Based on this finding, dosage reduction is proposed for patients with Child-Pugh C hepatic impairment. The proposed dosage reduction is considered acceptable based on the available data.

Efficacy

Evidence for efficacy is based primarily on the findings of Study AP26113-13-201 (the ALTA trial) which demonstrated a confirmed objective response rate of 55.5% for the proposed 90 → 180 mg daily dosage, with a median duration of response of 13.8 months. This response is clinically meaningful and durable.

Promising response rates were observed in patients with and without brain metastases at baseline. For the 90 → 180 mg daily dosage, patients with brain metastases at Baseline were numerically more likely to achieve an objective response to brigatinib compared to those without brain metastases.

The Phase I/II Study AP26113-11-101, reported similar response rates for patients receiving the dose proposed for registration, providing support for the efficacy outcomes observed in Study AP26113-13-201.

The submission lacks direct comparative data. There are limitations to the conclusions that can be drawn from the matching adjusted indirect comparisons with ceritinib and alectinib studies. The indirect comparisons are supportive of the efficacy of brigatinib but do not provide robust comparative data. Top-line results from the first planned interim analysis of the Phase III ALTA-1L trial were provided. The full study report for the ALTA-1L trial has not been submitted for evaluation so, for the purpose of this submission, the top-line results from the ALTA-1L trial are considered supportive of Study AP26113-13-201 (ALTA trial).

Safety

The safety database for brigatinib is limited in terms of patient numbers and duration, but is considered adequate in the context of the disease morbidity and mortality.

Overall, brigatinib appears to be reasonably tolerated, with a discontinuation rate of 6.4% across the whole safety population and 10% in the 90 → 180 mg daily dose group of Study AP26113-13-201 (ALTA trial).

Early onset pulmonary events are a notable concern, occurring in 6% of patients in Study AP26113-13-201. All of these events occurred at the 90 mg daily dosage, providing some support for the proposed 90 → 180 mg daily dosing regimen. The risk of early onset pulmonary events appears to be higher in patients aged ≥ 65 years.

Other notable safety issues including hypertension, bradycardia, vision disturbance, elevated CPK, peripheral neuropathy and elevated pancreatic enzymes have been addressed in Section 4.4 of the draft PI. Elevations of hepatic enzymes were common, with the majority below CTCAE Grade 3. Elevation of hepatic enzymes has been included in the EU's Summary of Product Characteristics (SmPC) on the basis that safety data for brigatinib are limited and hepatotoxicity is a known safety concern with other ALK inhibitors. Similar guidance regarding elevation of hepatic enzymes should be added to the Australian PI.

Brigatinib can cause serious/severe toxicities and there are residual uncertainties relating to the limited safety dataset, but these risks are considered acceptable given the nature of the disease and the durable responses observed in Study AP26113-13-201. Treatment-related toxicities are generally manageable with supportive care and/or dose adjustments.

The limited size and duration of the safety database means that uncommon or rare events may not have been identified. The ongoing Phase III study will further inform the safety profile of brigatinib.

Dosing

Clinical findings from Study AP26113-13-201 (the ALTA trial) support the proposed 90 → 180 mg daily dosage regimen. The ORR was numerically higher for the proposed 90 → 180 mg daily dosing regimen compared to 90 mg QD. Intracranial ORR data and progression free survival data from Study AP26113-13-201 were also supportive of the 90 → 180 mg dosage regimen.

The 90 → 180 mg daily dosage was proposed in response to the identified risk of early onset pulmonary events. Study AP26113-13-201 did not show an increased risk of early onset pulmonary events when progressing from 90 mg to 180 mg daily. The higher dosage was associated with a higher rate of treatment discontinuations and treatment emergent AEs of Grade 3 or higher, but this is considered acceptable in the context of the seriousness of the disease and the response rates demonstrated in Study AP26113-13-201.

Deficiencies of the data

The lack of direct comparative data limits the conclusions that can be drawn regarding the efficacy and safety of brigatinib. Preliminary results from the Phase III ALTA-1L trial (Study AP26113-13-301) comparing brigatinib to crizotinib in patients with ALK+ NSCLC are promising but the clinical study report has not yet been evaluated. The results of this study will further inform the efficacy and safety of brigatinib. The primary outcome is progression free survival assessed by blinded ICR. The planned primary completion date is mid-2019.

The majority of patients in Study AP26113-13-201 had Stage IV disease (97.7% overall, 98.2% in Arm B), so data for Stage III disease are very limited.

There are no efficacy or safety data in patients with hepatic impairment or severe renal impairment.

Conclusion

With regard to clinical data, Study AP26113-13-201 demonstrated clinically meaningful and durable tumour responses in patients with advanced (predominantly Stage IV) ALK+ NSCLC previously treated with crizotinib. Intracranial responses were also promising. There is some residual uncertainty regarding the clinical benefit of brigatinib relative to approved therapies for advanced ALK+ NSCLC due to a lack of direct comparative data; however, considering the nature of the disease and the supportive evidence from the

indirect comparisons and the preliminary results from the Phase III study, the response rates observed in Study AP26113-13-201 are considered likely to predict clinical benefit.

There are substantial safety risks with brigatinib treatment, but these can generally be managed with appropriate clinical monitoring, supportive treatment and/or dose modifications.

Proposed action

In assessing this application for registration, it is relevant to note that provisional registration was not available at the time that the application for registration was submitted. It is also noted that the Phase III ALTA-1L trial is in progress and will provide further data on the efficacy and safety of brigatinib.

The benefit-risk of brigatinib is considered favourable based on the durable ORR rate in Study AP26113-13-201 (ALTA trial) and the observed safety profile. The proposed indication should specify that the decision to register this medicine has been made on the basis of ORR and duration of response in a non-comparative study, and that the sponsor is required to submit further clinical data to confirm the efficacy and safety of brigatinib. These changes are necessary because the assessment of efficacy in this submission is based primarily on tumour response in a non-comparative study, with supportive evidence from indirect comparisons and preliminary results from the Phase III study.

Request for ACM advice

At this stage, there are no outstanding questions requiring expert advice, so the Delegate does not propose to seek advice from Advisory Committee on Medicines (ACM).

Advisory Committee Considerations[16]

The Delegate did not refer this application to the ACM for advice.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Alunbrig (brigatinib) film coated tablets 30 mg, 90 mg or 180 mg, indicated for:

> *Alunbrig is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib.*
>
> *The approval of this medicine is based on objective response rate and duration of response in a non-comparative study.*

[16] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Specific conditions of registration applying to these goods

- Alunbrig (brigatinib) is to be included in the Black Triangle Scheme. The PI and CMI for Alunbrig must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Alunbrig (brigatinib) EU-RMP (version 4.3, dated 19 June 2018, DLP 31 May 2016), with ASA (October 2018), included with submission PM-2018-00586-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs). Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.
- Submit the clinical study report for the Phase III Study ALTA-1L when available.
- Batches of brigatinib drug substance which are used to make batches of Alunbrig tablets supplied in Australia must meet a limit for Residue on Ignition of not more than 0.15% w/w.

  Batches of brigatinib drug substance which are used to make batches of Alunbrig tablets supplied in Australia must have an assay in the range 98.0 to 102.0% w/w (anhydrous and solvent free).

Attachment 1. Product Information

The PI for Alunbrig approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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