20 September 2018
EMA/696925/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Alunbrig

International non-proprietary name: brigatinib

Procedure No. EMEA/H/C/004248/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALK	anaplastic lymphoma kinase
ALK+	ALK-positive
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé (France)
aPTT	activated partial thromboplastin time
ARIAD	ARIAD Pharmaceuticals, Inc.
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-120}	area under the curve from time 0 to 120 hours postdose
AUC_{0-24}	area under the curve between 0 to 24 hours postdose at steady state
$AUC_{0-\infty}$	area under the curve from time 0 to infinity
$AUC_{0-\tau}$	area under the curve from time 0 to end of dosing interval
$AUC_{0-\tau,ss}$	area under the curve from time 0 to end of dosing interval at steady state
BCRP	Breast Cancer Resistance Protein
BCS	Biopharmaceutics Classification System
BID	twice daily
BSEP	Bile Salt Export Pump
C2BBe1	human colon carcinoma cell line
C_{ave}	average concentration
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL/F	Apparent clearance unadjusted for bioavailability
CL_{CR}	creatinine clearance
C_{max}	maximum plasma concentration
CMC	Chemistry, Manufacturing, and Controls
CNS	central nervous system
CPK	creatine phosphokinase
CPP	Critical process parameter
CQA	Critical Quality Attribute
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome P450
DBP	diastolic blood pressure
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DoE	Design of experiments
DSC	Differential Scanning Calorimetry
DVS	Dynamic Vapour Sorption
EAP	expanded access protocol
EC	European Commission
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EML4	echinoderm microtubule-associated protein-like 4
EOP1	end of phase 1
EOPE	early onset pulmonary event
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration (United States)
FISH	fluorescence in situ hybridization

FT-IR	Fourier Transform Infrared Spectroscopy
GeoMean	geometric mean
GI	gastrointestinal
Grade	Severity of the AE by Grades 1 through 5; Grade 1 = Mild AE; Grade 2 = Moderate AE; Grade 3 = Severe AE; Grade 4 = Life-threatening or disabling AE; Grade 5 = Death related to AE
HDPE	High Density Polyethylene
HNSTD	highest non severely toxic dose
HPLC	High performance liquid chromatography
HR	hazard ratio
HRQoL	health-related quality-of-life
HS-GC	Headspace Capillary Gas Chromatography
IC50	50% maximum inhibitory concentration
IC90	90% maximum inhibitory concentration
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
ICP-OES	Inductively coupled plasma optical emission spectrometry
ILD	interstitial lung disease
iPSP	initial proposed pediatric study plan
IR	immediate release
IRC	independent review committee
ITT	Intent-to-treat
KD	kinase domain
KF	Karl Fischer titration
KM	Kaplan-Meier
LFT	liver function tests
MAA	Marketing Authorization Application
MATE1	Multidrug and Toxin Extrusion Protein 1
MATE2K	Multidrug and Toxin Extrusion Protein 2K
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MHRA	Medicines and Healthcare Product Regulatory Agency (UK)
MPA	Medical Products Agency (Sweden)
ms	millisecond
MS	Mass Spectrometry
MTD	maximum tolerated dose
MTT	mean transit time
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute (of the United States)
Ng	nanogram
NGS	next generation sequencing
nM	nanomolar
NMR	Nuclear Magnetic Resonance
NOAEL	no observed adverse effect level
NSCLC	non-small cell lung cancer
OAT1	Organic Anion Transporter 1
OAT3	Organic Anion Transporter 3
OCT1	Organic Cation Transporter 1
OCT2	Organic Cation Transporter 2
OR	odds ratio
ORR	objective response rate
OS	overall survival
PCTFE	Poly-chloro-tri-fluoro-ethylene
PD	pharmacodynamic
PD-1	programmed cell death
PD-L1	programmed death-ligand 1
PFS	progression-free survival
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic(s)
PR	partial response
QbD	Quality by design
QD	once-daily

QLQ-C30	Quality of Life Questionnaire C30
QRS interval	corresponds to depolarization of the right and left ventricles of heart
QT	QT interval; a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc	heart rate-corrected QT interval (calculated)
QTcF	QT interval corrected (Fridericia)
QTPP	Quality target product profile
RECIST	Response Evaluation Criteria in Solid Tumors (version 1.1)
Ref	reference treatment for hazard ratio comparison
RH	Relative Humidity
RP2D	recommended phase 2 dose
RP-HPLC	Reverse Phase High performance liquid chromatography
SAE	serious adverse event
SAP	statistical analysis plan
SAWP	Scientific Advice Working Party
SBP	systolic blood pressure
SCE	Summary of Clinical Efficacy
SD	stable disease
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TAMC	Total Aerobic Microbial Count
TEAE	Treatment emergent adverse event
TKI	tyrosine kinase inhibitor
TYMC	Total Combined Yeasts/Moulds Count
ULN	upper limit of normal
US	United States
UV	X-Ray Powder Diffraction
V1/F	Apparent volume of distribution unadjusted for bioavailability
Vz/F	Apparent volume of distribution during terminal phase unadjusted for bioavailability

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Takeda Pharma A/S submitted on 3 February 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Alunbrig, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following 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.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that brigatinib was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

New active Substance status

The applicant requested the active substance brigatinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 21 November 2013. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Sinan B. Sarac Co-Rapporteur: Nithyanandan Nagercoil

The application was received by the EMA on	3 February 2017
The procedure started on	23 February 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	11 May 2017
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	12 May 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	29 May 2017
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 June 2017
The applicant submitted the responses to the CHMP consolidated List of Questions on	10 August 2017
The following GMP and GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– GCP inspection at a CRO facility in USA and two investigator sites, located in Germany and Denmark were conducted between June-July 2017 in connection with the conduct of pivotal trial with protocol number AP26113-13-201. The outcome of the inspection carried out was issued on	28 September 2017
– A GMP inspection at three sites located in the USA, responsible for manufacture, packaging and quality control testing of the finished product conducted between 10-14 July 2017. The outcome of the inspection carried out was issued on	18 and 31 October 2017
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	19 September 2017
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 September 2017
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	12 October 2017
The applicant submitted the responses to the CHMP List of Outstanding Issues on	21 December 2017
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	10 January 2018
The Rapporteurs circulated the updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	18 January 2018
The CHMP agreed on a 2nd list of outstanding issues to be sent to the applicant on	25 January 2018
The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on	20 August 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP members on	29 August 2018
The Rapporteurs circulated the updated Joint Assessment Report on the responses to	13 September

the 2nd List of Outstanding Issues to all CHMP members on	2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Alunbrig on	20 September 2018

2. Scientific discussion

2.1. Problem statement

Despite other therapies being available or investigated for NSCLC more generally (e.g., chemotherapy, immunotherapy, and anti-angiogenesis therapy), ESMO treatment guidelines[1] recommend that first-line treatment with crizotinib is preferred for patients with ALK+ NSCLC. In patients who progress after crizotinib, further treatment with second generation ALK-inhibitor therapy (such as ceritinib, which is currently approved in the EU) is recommended.

2.1.1. Disease or condition

Alunbrig is intended 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.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Lung cancer is one of the most common cancers in the world (1.8 million new cases in 2012), 12.9% of all new cancers worldwide[2].

Estimates of the frequency of ALK rearrangement in the overall population of NSCLC patients range from 2% to 7%[3,4]), which represent approximately 7,000-25,000 ALK+ NSCLC patient in the US and 5,800-20,000 patients in the EU in 2016.

2.1.3. Biologic features/Aetiology and pathogenesis

ALK is a tyrosine kinase encoded on chromosome 2 and is primarily involved in developmental processes and expressed at low levels in adults[5]. The first genetic rearrangement of ALK seen in NSCLC involved a fusion between the echinoderm microtubule-associated protein-like 4 (EML4) gene and the ALK tyrosine kinase domain. EML4-ALK has the capacity to transform fibroblasts grown in culture and as subcutaneous xenografts to induce tumor formation[6]. Since then, a number of additional ALK fusion partners have been described in NSCLC that are believed to result in aberrant signaling and oncogenic transformation[7] [8]. ALK rearrangements are more common among patients

[1] Novello S, Barlesi F, Califano R, et al, ESMO Guidelines Committee. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27 (suppl 5):v1-v27.
[2] Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide. Lyon, France: International Agency for Research on Cancer 2013 [cited 2016 11 July]; available from: http://globocan.com.iard.fr]
[3] Kwak E, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med. 2010;363(18):1693-703
[4] Wong D, Leung EL, So KK, et al. The EML4-ALK fusion gene is involved in various histological types of lung cancers from nonsmokers with wild-type EGFR and KRAS. Cancer. 2009;115:1723-33.
[5] Camidge D, Doebele RC. Treating ALK-positive lung cancer-early successes and future challenges. Nat Rev Clin Oncol. 2012;9(5):268-77
[6] Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature. 2007;448(7153):561-6.
[7] Rikova K, Guo A, Zeng Q, et al. Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. Cell. 2007;131(6):1190-203.

with adenocarcinoma histology, patients who have never smoked, and patients who have wild-type EGFR and v-Ki-ras2 Kirsten rat sarcoma viral oncogene homologue (KRAS)[9].

2.1.4. Clinical presentation, diagnosis and stage / prognosis

Approximately, one-third of the patients with Stage IIIA disease are considered operable. However, the majority of patients with Stage IIIA/B have inoperable (unresectable) disease, and are amenable to receiving curative intention chemoradiation treatment. The biological characteristics of locally advanced, Stage III disease are poorly defined; the clinical characteristics associated with prognosis are nodal station involvement, size of primary tumor, baseline pulmonary function, gender, presence or absence of significant weight loss, and performance status (PS).

Pathological diagnosis based on tumour samples includes immunohistochemistry (IHC) to identify adenocarcinoma or squamous cell carcinoma. Molecular testing should be carried out to determine genetic alterations such as EGFR mutations and ALK rearrangements which determine choice of targeted treatment. The break-apart fluorescence in situ hybridisation (FISH) test remains a core approach to detect ALK rearrangements

2.1.5. Management

While the standard treatment algorithm for unselected NSCLC patients has historically involved front-line treatment with chemotherapy, recent clinical studies have demonstrated that patients with ALK+ locally advanced or metastatic NSCLC respond well to treatment with the ALK inhibitor crizotinib[10].

Approval of **crizotinib** was based on results from two single-arm studies[11].

In one study (N = 136) with a median duration of treatment of 22 weeks, the objective response rate (ORR) was 50% (95% CI: 42, 59%) and the median duration of response was 41.9 weeks. In the other study (N = 119) with a median duration of treatment of 32 weeks, the ORR was 61% (95% CI: 52, 70%) and the median duration of response was 48.1 weeks. In a randomized study of crizotinib versus chemotherapy (pemetrexed or docetaxel) in ALK+ NSCLC patients, a statistically significant improvement in progression–free survival (PFS) was observed in patients treated with crizotinib (hazard ratio [HR] 0.49 [95% CI: 0.37 0.64], p<0.001). In patients treated with crizotinib, median PFS and overall survival (OS) were 7.7 months and 20.3 months, respectively[12]. In a separate randomized study of crizotinib against pemetrexed-platinum doublet chemotherapy in patients with advanced, previously untreated non-squamous ALK+ NSCLC, median PFS was 10.9 months in the crizotinib arm and 7.0 months in the chemotherapy arm (HR 0.45 [95% CI: 0.35–0.60], p<0.001)[13].

Therefore, Crizotinib is currently recommended as first-line therapy for ALK positive NSCLC. Although crizotinib is an effective treatment for ALK+ NSCLC, 26 to 35% of patients fail to respond[14], and the majority of patients progress within 1 year, with multiple mechanisms of resistance having been identified. ALK-dependent mechanisms of resistance, observed in approximately 30% of patients[15], include the acquisition of secondary mutations in ALK that interfere with crizotinib binding, and/or amplification of the ALK fusion gene. More than 10 secondary mutations in ALK have been associated

[8] Takeuchi K, Choi YL, Togashi Y, et al. KIF5B-ALK, a novel fusion oncokinase identified by an immunohistochemistry-based diagnostic system for ALK-positive lung cancer. Clin Cancer Res.2009;15(9):3143-9.
[9] Camidge D, Doebele RC. Treating ALK-positive lung cancer-early successes and future challenges. Nat Rev Clin Oncol. 2012;9(5):268-77.
[10] Xalkori. crizotinib EU product information. Pfizer Limited, Sandwich, Kent, United Kingdom. 2016.
[11] Xalkori. crizotinib EU product information. Pfizer Limited, Sandwich, Kent, United Kingdom. 2016.
[12] Xalkori. crizotinib EU product information. Pfizer Limited, Sandwich, Kent, United Kingdom. 2016.
[13] Solomon B, Mok T, Kim D-W, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med. 2014;371(23):2167-77
[14] Xalkori. crizotinib EU product information. Pfizer Limited, Sandwich, Kent, United Kingdom. 2016.
[15] Katayama R, Lovly CM, Shaw AT. Therapeutic targeting of anaplastic lymphoma kinase in lung cancer: a paradigm for precision cancer medicine. Clin Cancer Res. 2015;21:2227-35.

with crizotinib resistance in patients, with the most common being L1196M and G1269A[16] [17]. The central nervous system (CNS) is the first site of progression in approximately 50% of patients[18] [19], suggesting inadequate penetration of crizotinib into the brain (i.e., pharmacologic failure) as the primary cause of resistance in these patients. Therefore, an ALK inhibitor that can overcome secondary resistance mutations in ALK and is less susceptible to pharmacologic failure may be required to overcome resistance.

Recently, two other ALK inhibitors, **ceritinib and alectinib**, have become available for NSCLC patients with ALK rearrangements who have disease progression or are intolerant to crizotinib. Also, ceritibib and alectinib are authorized as monotherapy for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). Also, ceritibib and alectinib are authorized as monotherapy for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).ALK secondary mutations associated with clinical resistance to ceritinib and alectinib have also been identified, including L1152R and F1174C/V for ceritinib, I1171N/T/S for alectinib, and G1202R for both agents[20] [21] [22] [23] [24] [25]. A highly potent ALK inhibitor that is both CNS-penetrant and well tolerated is still needed to better treat patients with oncogenic ALK-activating mutations and rearrangements. Up to 50% of patients with NSCLC will have brain metastases during the course of the disease, resulting in reduced quality of life and limited survival[26] [27]. Survival of patients with brain metastases has been considered very poor [28],[29], with risk of death and significant impairments in quality of life being increased by a factor of 4 [30], [31]. The median survival of patients with untreated brain metastases is reported to be 1 to 3 months [32], [33], [34].

[16] Katayama R, Lovly CM, Shaw AT. Therapeutic targeting of anaplastic lymphoma kinase in lung cancer: a paradigm for precision cancer medicine. Clin Cancer Res. 2015;21:2227-35.
[17] Toyokawa G, Seto T. Updated evidence on the mechanisms of resistance to ALK inhibitors and strategies to overcome such resistance: clinical and preclinical data. Oncol Res Treat. 2015;38:291-8.
[18] Costa D, Shaw AT, Ou SH, et al. Clinical experience with crizotinib in patients with advanced ALK-rearranged non-small-cell lung cancer and brain metastases. J Clin Oncol. 2015;33:1881-8.
[19] Weickhardt A, Scheier B, Burke JM, et al. Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. J Thorac Oncol. 2012;7:1807-14.
[20] Friboulet L, Li N, Katayama R, et al. The ALK inhibitor ceritinib overcomes crizotinib resistance in non-small cell lung cancer. Cancer Discovery. 2014;4:662-73.
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[22] Ou S, Greenbowe J, Khan ZU, et al. I1171 missense mutation (particularly I1171N) is a common resistance mutation in ALK-positive NSCLC patients who have progressive disease while on alectinib and is sensitive to ceritinib. Lung Cancer. 2015b;88:231-4.
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[31] Patchell R, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med. 1990;322:494-500.
[32] Flannery T, Suntharalingam M, Kwok Y, et al. Gamma knife stereotactic radiosurgery for synchronous versus metachronous solitary brain metastases from non-small cell lung cancer. Lung Cancer. 2003;42:327-33.
[33] Louie A, Rodrigues G, Yaremko B, et al. Management and prognosis in synchronous solitary resected brain metastasis from non-small cell lung cancer. Clin Lung Cancer. 2009;10:174-9.
[34] Penel N, Brichet A, Prevost B, et al. Prognostic factors of synchronous brain metastases from lung cancer. Lung Cancer. 2001;33:143-54.

About the product

Brigatinib is a tyrosine kinase inhibitor that targets ALK, c-ros oncogene 1 (ROS1), and insulin like growth factor 1 receptor (IGF 1R).Brigatinib inhibited autophosphorylation of ALK and ALK mediated phosphorylation of the downstream signalling protein STAT3 in in vitro and in vivo assays (SmPC, section 5.1)..

Brigatinib inhibited the in vitro proliferation of cell lines expressing EML4 ALK and NPM ALK fusion proteins and demonstrated dose dependent inhibition of EML4 ALK positive NSCLC xenograft growth in mice. Brigatinib inhibited the in vitro and in vivo viability of cells expressing mutant forms of EML4-ALK associated with resistance to ALK inhibitors, including G1202R and L1196M (SmPC, section 5.1).

The applicant applied for the following 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.

The recommended indication for approval is: 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.

Brigatinib is available as 30 mg, 90 mg and 180 mg film-coated tablets. The recommended starting dose is 90 mg orally once daily for the first 7 days, then 180 mg orally once daily (SmPC, section 4.2).

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

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

Treatment should continue as long as clinical benefit is observed.

Dose adjustments

Dosing interruption and/or dose reduction may be required based on individual safety and tolerability.

Alunbrig dose modification levels are summarised in Table 1.

Table 1: Recommended Alunbrig dose reduction levels

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

Alunbrig should be permanently discontinued if patient is unable to tolerate the 60 mg once daily dose.

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

Table 2: Recommended Alunbrig dose modifications for adverse reactions

Adverse reaction	**Severity***	**Dose modification**
Interstital lung disease	Grade 1	• If event occurs during the first 7 days of treatment, Alunbrig should be withheld until recovery to baseline, then resumed at same dose level and not escalated to

Adverse reaction	Severity*	Dose modification
(ILD)/pneumonitis		180 mg once daily. • If ILD/pneumonitis occurs after the first 7 days of treatment, Alunbrig should be withheld until recovery to baseline, then resumed at same dose level. • If ILD/pneumonitis recurs, Alunbrig should be permanently discontinued.
	Grade 2	• If ILD/pneumonitis occurs during the first 7 days of treatment, Alunbrig should be withheld until recovery to baseline, then resumed at next lower dose level as described in Table 1 and not escalated to 180 mg once daily. • If ILD/pneumonitis occurs after the first 7 days of treatment, Alunbrig should be withheld until recovery to baseline. Alunbrig should be resumed at next lower dose level as described in Table 1. • If ILD/pneumonitis recurs, Alunbrig should be permanently discontinued.
	Grade 3 or 4	• Alunbrig should be permanently discontinued.
Hypertension	Grade 3 hypertension (SBP ≥ 160 mmHg or DBP ≥ 100 mmHg, medical intervention indicated, more than one anti-hypertensive medicinal product, or more intensive therapy than previously used indicated)	• Alunbrig should be withheld until hypertension has recovered to Grade ≤ 1 (SBP <140 mmHg and DBP <90 mmHg), then resumed at same dose. • If Grade 3 hypertension recurs, Alunbrig should be withheld until hypertension has recovered to Grade ≤ 1 then resumed at the next lower dose level per Table 1 or permanently discontinued
	Grade 4 hypertension (life threatening consequences, urgent intervention indicated)	• Alunbrig should be withheld until hypertension has recovered to Grade ≤ 1 (SBP <140 mmHg and DBP <90 mmHg), then resumed at the next lower dose level per Table 1 or permanently discontinued. • If Grade 4 hypertension recurs, Alunbrig should be permanently discontinued.
Bradycardia (HR less than 60 bpm)	Symptomatic bradycardia	• Alunbrig should be withheld until recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above. • If a concomitant medicinal product known to cause bradycardia is identified and discontinued, or its dose is adjusted, Alunbrig should be resumed at same dose upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above. • If no concomitant medicinal product known to cause

Adverse reaction	Severity*	Dose modification
		bradycardia is identified, or if contributing concomitant medications are not discontinued or dose modified, Alunbrig should be resumed at the next lower dose level per Table 1 upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above.
	Bradycardia with life-threatening consequences, urgent intervention indicated	• If contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, Alunbrig should be resumed at the next lower dose level per Table 1 upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above, with frequent monitoring as clinically indicated. • Alunbrig should be permanently discontinued if no contributing concomitant medicinal product is identified. • Alunbrig should be permanently discontinued in case of recurrence.
Elevation of CPK	Grade 3 elevation of CPK (>5.0 × ULN)	• Alunbrig should be withheld until recovery to Grade ≤ 1 (≤2.5 × ULN) or to baseline, then resumed at the same dose. • If Grade 3 elevation of CPK recurs, Alunbrig should be withheld until recovery to Grade ≤ 1 (≤2.5 × ULN) or to baseline, then resumed at the next lower dose level per Table 1.
	Grade 4 elevation of CPK (>10.0 × ULN)	• Alunbrig should be withheld until recovery to Grade ≤ 1 (≤2.5 × ULN) or to baseline, then resumed at the next lower dose level per Table 1.
Elevation of lipase or amylase	Grade 3 elevation of lipase or amylase (>2.0 × ULN)	• Alunbrig should be withheld until recovery to Grade ≤ 1 (≤1.5 × ULN) or to baseline, then resumed at same dose. • If Grade 3 elevation of lipase and amylase recurs, Alunbrig should be withheld until recovery to Grade ≤ 1 (≤1.5 × ULN) or to baseline, then resumed at the next lower dose level per Table 1.
	Grade 4 elevation of lipase or amylase (>5.0 x ULN)	• Alunbrig should be withheld until recovery to Grade ≤ 1 (≤1.5 × ULN), then resumed at the next lower dose level per Table 1.
Elevation of hepatic enzymes	Grade ≥ 3 elevation (>5.0 × ULN) of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST)	• Alunbrig should be witheld until recovery to baseline or less than or equal to 3 × ULN, then resumed at next lower dose per Table 1.

Adverse reaction	Severity*	Dose modification
	with bilirubin ≤ 2 × ULN	
	Grade ≥ 2 elevation (>3 × ULN) of ALT or AST with concurrent total bilirubin elevation >2 × ULN in the absence of cholestasis or haemolysis	• Alunbrig should be permanently discontinued.
Hyperglycaemia	For Grade 3 (greater than 250 mg/dL or 13.9 mmol/L) or greater	• If adequate hyperglycaemic control cannot be achieved with optimal medical management, Alunbrig should be withheld until adequate hyperglycaemic control is achieved. Upon recovery, Alunbrig may either be resumed at the next lower dose per Table 1 or permanently discontinued.
Visual Disturbance	Grade 2 or 3	• Alunbrig should be withheld until recovery to Grade 1 or baseline, then resumed at the next lower dose level per Table 1.
	Grade 4	• Alunbrig should be permanently discontinued.
Other adverse reactions	Grade 3	• Alunbrig should be withheld until recovery to baseline, then resumed at the same dose level. • If the Grade 3 event recurs, Alunbrig should be withheld until recovery to baseline, then resumed at the lower dose level as per Table 1 or permanently discontinued.
	Grade 4	• Alunbrig should be withheld until recovery to baseline, then resumed at the next lower dose level as per Table 1. • If the Grade 4 event recurs, Alunbrig should be withheld until recovery to baseline, then resumed at the next lower dose level as per Table 1 or permanently discontinued.
bpm = beats per minute; CPK = Creatine Phosphokinase; DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure; ULN = upper limit of normal		

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

Type of Application and aspects on development

In 2013, ARIAD engaged in scientific advice meetings with Medicines and Health Products Regulatory Agency (MHRA), Medical Products Agency (MPA), Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM), EMA Scientific Advice Working Party (SAWP)/CHMP. European agencies provided similar feedback to obtain preliminary data on an effect of food on the PK, and safety of brigatinib prior to Study AP26113 13-201. Results from all completed clinical pharmacology studies requested by regulatory agencies are included in the present MAA.

Regulatory Advice on the Phase 2 Trial (AP26113-13-201, ALTA)

The study design aspects of the phase 2 Study AP26113-13-201 were discussed with regulatory agencies, including the patient eligibility criteria, primary endpoint, sample size calculation, and secondary endpoints. Initially, the study design of Study AP26113-13-201 only included a single brigatinib 180 mg QD treatment arm with a sample size of approximately 150 patients. The study was subsequently amended to a randomized study that includes two arms: (1) 90 mg QD continuously and (2) 180 mg QD after a 7-day lead-in at 90 mg QD, with an increased total sample size of 218 patients (actual enrollment was 222 patients).

Regulatory Advice on the Phase 3 Study, AP26113-13-301 (ALTA 1L)

In November 2013, according to the feedback received from EMA/CHMP/SAWP, the proposed randomized phase 3 study (Study AP26113-13-301) comparing brigatinib to crizotinib with PFS as primary endpoint could potentially serve to support the transformation of the conditional MA into a regular approval in ALK+ NSCLC patients previously treated with crizotinib. However, the Agencies commented on the proposed planned interim analyses and the overall size of the study (i.e., 1050 patients) as being challenging to complete given the size of the patient population. ARIAD has taken this feedback into consideration, and in light of the emerging data from Study AP26113-13-201, adjusted the study sample size to enroll approximately 270 patients, and two interim analyses are planned after approximately 50% and 75% of the total expected events (progression or death) have been observed in Study AP26113-13-301.

General comments on compliance with GMP, GLP, GCP

GMP:

Active substance:

The EU batch releaser Penn Pharmaceutical Services Ltd (United Kingdom) has provided a QP declaration confirming that manufacture of the drug substance is performed in accordance with the detailed guidelines on good manufacturing practices for starting materials, as defined in “Volume 4- Medicinal Products for Human and Veterinary Use: Good Manufacturing Practice/Part II – Basic Requirements for Active Substances used as the Starting Materials”.

The QP declaration is dated 23 January, 2017 and signed by an EU Qualified Person. The presented QP declaration is considered acceptable.

Final product:

GMP certificates have been included in the file. The European Medicines Agency Compliance and Inspection Sector has reviewed the manufacturer information contained in the application form (Module 1) and available from the EEA National Competent Authorities and determined that all relevant sites have valid manufacturing authorizations or valid GMP certificates as appropriate, with the exception of 3 sites for which an inspection has been agreed by the CHMP.

A GMP inspection at three sites, responsible for manufacture, packaging and quality control testing of the finished product conducted between 10-14 July 2017. The outcome of the inspection carried out was issued on 18 and 31 October 2017.

GCP:

GCP inspections at a CRO facility in USA and two investigator sites, located in Germany and Denmark were conducted between June-July 2017 in connection with the conduct of pivotal trial with protocol number AP26113-13-201. The outcome of the inspection carried out was issued on 28 September 2017.

All the studies included in this submission were conducted in accordance with Good Clinical Practice (GCP) guidelines. The appropriate Ethics Committees and Institutional Review Boards reviewed and approved all the studies.

GLP

All safety pharmacology *in vivo* studies as well as the pivotal toxicology studies were conducted in compliance with Good Laboratory Practice (GLP) Regulations.

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the fact that treatments are already authorised in the applied indication for brigatinib, furthermore, brigatinib does not offer a novel mechanism of action and there is no indication that the safety profile will be improved compared to authorised treatments.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 30, 90 or 180 mg of brigatinib as active substance.

Other ingredients are:

Tablet core: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (type A), silica colloidal hydrophobic and magnesium stearate.

Tablet coating: talc, macrogol, polyvinyl alcohol and titanium dioxide.

The product is available in round wide mouth high density polyethylene (HDPE) bottles with two piece polypropylene child resistant screw cap closures with foil induction seal liners. Each bottle contains an HDPE canister containing a molecular sieve desiccant.

The product is also available in clear thermoformable polychlorotrifluoroethylene (PCTFE) blisters with heat sealable paper laminated foil lidding in a carton. Both packaging formats are described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of brigatinib is 5-chloro-2-*N*-{4-[4-(dimethylamino)piperidin-1-yl]-2-methoxyphenyl}-4-*N*-[2-(dimethylphosphoryl)phenyl]pyrimidine-2,4-diamine corresponding to the molecular formula $C_{29}H_{39}ClN_7O_2P$. It has a relative molecular mass of 584.9 and the following structure:

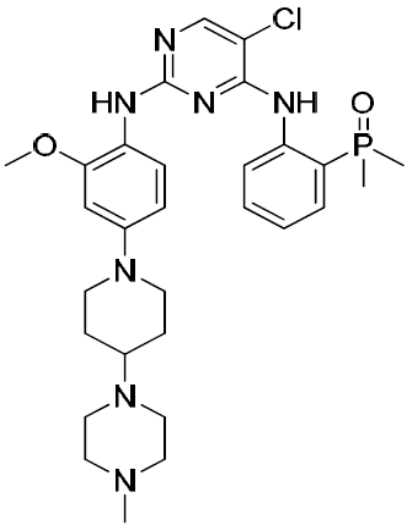


Figure 1: active substance structure

The chemical structure of brigatinib was elucidated by a combination of ^{1}H, ^{13}C and ^{31}P nuclear magnetic resonance spectroscopy (NMR), mass spectrometry (MS), single crystal X-ray crystallography, elemental analysis, Fourier transform infrared (FT-IR) spectroscopy, and ultraviolet (UV) spectroscopy.

The solid state properties of the active substance were measured by differential scanning calorimetry (DSC), thermogravimetric analysis (DVS) and x-ray powder diffraction (XRPD).

The active substance is an off-white to beige, non-hygroscopic solid. Brigatinib is considered a Biopharmaceutics Classification System (BCS) Class 1 substance based on relevant solubility and permeability studies. However, the finished product is not considered to be rapidly dissolving as defined by the Biopharmaceutics Classification System Guidance, which is discussed in the pharmaceutical development section of this report.

Brigatinib is achiral.

Polymorphism has been observed for brigatinib. Multiple solid forms and pseudo solid forms of brigatinib have been observed during solid state characterization studies. Solid Form A is the preferred form as it has shown to be anhydrous, non-hygroscopic, and physically and chemically stable under normal handling and storage conditions. Solid Form A is consistently produced utilizing the intended commercial manufacturing process. Once the most thermodynamically stable solid Form A is obtained, no conventional method has been found to convert it to another form *via* solvent mediated or solid-solid transition, exposure to elevated temperature or humidity, mechanical pressure or grinding. Moreover, development stability studies of the finished product demonstrate that no form change occurs following storage at 25 °C / 60% RH and 40 °C / 75% RH minimally through 6 months.

Manufacture, characterisation and process controls

Brigatinib is synthesized in numerous steps with multiple manufacturers.

The process involves synthesis between starting materials, intermediates to generate brigatinib (AP26113) crude, which is generated and isolated as a free base producing the active substance.

Following a thorough process risk-assessment of potential genotoxic impurities, focused control strategies have been identified in order to limit potential mutagenic impurities. These strategies include controls implicit in the design of the manufacturing process, in-process tests and parameters, and appropriate specifications for starting materials and intermediates.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Critical process parameters (CPPs), which impact the active substance critical quality attributes (CQAs) have been defined, and the overall control strategy is considered suitable.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. The modifications made to the manufacturing process throughout development are the basis for the proposed commercial process (Process B2) and include optimizations derived through a quality risk-based approach to bring more robust control of the CQAs of the active substance across a broader range of manufacturing scales i.e. lab, clinical, and the intended commercial scale. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The manufacturing process has been developed using a combination of conventional univariate studies and elements of QbD such as risk assessment and design of experiment (DOE) studies, which were conducted in order to enhance the process knowledge.

The active substance is packaged in a polyethylene continuous liner and an outer polyethylene bag which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for description (visual), identity (FT-IR, HPLC), assay (HPLC), impurities (HPLC), residual solvents (HS-GC), solid form confirmation (XRPD), heavy metals (colorimetric), particle size distribution (laser diffraction), residual metal catalysts (ICP-OES, ICP-MS, residue on ignition (Ph. Eur.) and water content (KF).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The absence of controls on microbiological enumeration for the active substance is acceptable based on water activity testing of registration batches.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from 27 pilot to production scale batches of the active substance were provided. The results were within the specifications and consistent from batch to batch.

The active substance specifications are based on the active substance CQAs which are appearance, identity, assay, impurities, residue on ignition, residual solvents, heavy metals, solid form and batch homogeneity.

Stability

Stability data from 7 batches manufactured at approximately a third of the commercial scale of the active substance from proposed manufacturers stored in the intended commercial package for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

Subsequent to the production of the above mentioned registration batches, the active substance manufacturing process was scaled up to the intended commercial scale. The increase in batch size from registration to commercial scale was performed using essentially the same equipment and processes with only minor changes relating to the increase in scale. All registration batches are considered representative of the commercial manufacturing process and of both manufacturers. Supportive data from 5 commercial scale batches of the active substance from proposed manufacturers stored in the intended commercial package for up to 12 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

No significant changes or trends were identified with the exception of specified impurity. Although reportable levels of the impurity show a slight increase during storage, all impurity results for all registration batches at all conditions are well within the qualified specification limit throughout the duration of testing. Linear regression analyses of the available stability data demonstrate that specified impurity will remain well within the specified limit with 95% confidence limit, minimally through 36 months of storage at the 25 °C / 60% RH condition. All tested parameters were within the specifications. The parameters tested are the same as for release. The analytical methods used were the same as for release and are stability indicating.

Photostability testing following the ICH guideline Q1B was performed on one batch. The photostability study performed on the active substance manufactured at the manufacturer is considered representative of the active substance at other manufacturers. All specifications were met for all tests and conditions.

Analytical data on one batch exposed as a solution or suspension to heat, acid, base, and hydrogen peroxide, were also provided. Brigatinib prepared in 2% aqueous hydrogen peroxide solution and stored at ambient conditions showed only minimal degradation after two hours. A solution in 1N HCl stored for 120 hours (5 days) at 80 °C exhibited moderate degradation. A suspension in 1N NaOH stored for 48 hours (2 days) at 80 °C exhibited significant degradation. The active substance prepared as an aqueous solution and stored for 120 hours (5 days) at 105 °C exhibited significant degradation.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 36 months with no special storage conditions in the proposed container, a polyethylene continuous liner and an outer polyethylene bag.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as white to off-white film-coated tablets in 30 mg, 90 mg and 180 mg dose strengths. Alunbrig 30 mg film-coated tablets are round, approximately 7 mm in diameter debossed with “U3” on one side and plain on the other. Alunbrig 90 mg film-coated tablets are oval, approximately 15 mm in length debossed with “U7” on one side and plain on the other side. Alunbrig 180 mg film-coated tablets are oval, approximately 19 mm in length debossed with “U13” on one side and plain on the other side. Strengths can be distinguished by their shape, size and debossing. The core tablets of the three dosage strengths are proportional in composition.

Pharmaceutical development of the finished product contains QbD elements. The quality target product profile (QTPP) is presented in Table 3.

Table 3: Alunbrig Quality Target Product Profile

Product Attribute	Development Target	Brigatinib Commercial Tablets
Route of Administration	Oral administration	Oral (Tablet)
Dose Strength	As required (will be determined in clinical trials)	30 mg, 90 mg, and 180 mg
Dosage Form	Immediate release solid dosage form	Immediate release tablet
Dosing Regimen	Once daily	90 mg QD or 90 mg daily for 1 week followed by dosing at 180 mg daily
Product Shelf Life and Storage Conditions	24-36 months at controlled room temperature. Degradation products below ICH qualification thresholds through-out shelf life	Minimally 12 months
Requirements to assure patient safety and efficacy at release and during shelf-life	All appropriate quality criteria including identification, assay, content uniformity, appearance, dissolution, degradants, water content, and microbial count	See Drug product CQAs (Table 2)
Manufacturing Process	Robust and reproducible process utilizing standard manufacturing equipment	Direct compression

The critical quality attributes (CQAs) are identified, along with the rationale for defining as CQAs.

The formulation and manufacturing development have been evaluated through the use of risk assessment and design of experiments to identify the critical product quality attributes and critical process parameters (CPPs). A risk analysis was performed in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes.

As discussed earlier in this report, brigatinib is a BCS class I substance exhibiting high solubility and permeability. However, the finished product does not meet the criteria for rapidly dissolving as defined by the Biopharmaceutics Classification System (BCS) Guidance. Therefore, no biowaiver claims are made.

Particle size distribution of the active substance was determined during development using dry dispersion laser diffraction. The available data demonstrate the capacity of the intended commercial manufacturing process to produce active substance batches exhibiting consistent particle size distribution at both manufacturing sites. The data presented show that the active substance particle size distribution has no effect on the finished product content uniformity. Additional clinical data demonstrate that the performance of oral brigatinib is dependent on the rate of brigatinib absorption in the gastrointestinal tract rather than being limited by disintegration of the dosage form or dissolution of the active substance in the stomach.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The active substance has been assessed for compatibility with a range of commonly used pharmaceutical excipients suitable for immediate release solid oral dosage forms. An excipient compatibility study using twelve excipients was conducted with binary and ternary mixtures supporting the choice of excipients.

Initial clinical studies were performed using Formulation-0. Subsequently, a 30 mg tablet formulation, Formulation-1, was developed to accommodate continued clinical trials and the intended commercial dosage form. Minor formulation optimisations led to Formulation-2 allowed for improvements in manufacturability, as did Formulation-3. Formulation-3 is the intended commercial formulation used at

finished product manufacturing sites for the manufacture of 30 mg, 90 mg, and 180 mg tablets. This formulation was used in Phase 3 clinical studies. *In vitro* dissolution studies to compare batches manufactured at different sites showed equivalent dissolution profiles.

The discriminatory power of the dissolution method has been demonstrated in terms of its ability to detect differences in formulation and process variability.

The product is available in round wide mouth high density polyethylene (HDPE) bottles with two piece polypropylene child resistant screw cap closures with foil induction seal liners. Each bottle contains an HDPE canister containing a molecular sieve desiccant.

The product is also available in clear thermoformable polychlorotrifluoroethylene (PCTFE) blisters with heat sealable paper laminated foil lidding in a carton. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

Alunbrig film-coated tablets are manufactured from a common blend by a standard manufacturing process.

The finished product manufacturing sites incorporate slightly different equipment, but the equipment class, operating principles and each unit of operation are comparable for the manufacturers.

Proven acceptable ranges (PARs) have been defined for the medicinal product. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs. However, no regulatory flexibility (variation of multiple parameters at a time which would constitute a design space) is claimed.

It has been demonstrated during production of clinical and development batches that the manufacturing process is capable of producing the finished product of the intended quality in a reproducible manner. A process validation scheme has been provided which is deemed acceptable. Process validation will be carried out on a minimum of three commercial scale batches of each of the tablet strengths prior to commercialization. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual), identity (FT-IR, RP-HPLC), assay (RP-HPLC), degradation products (RP-HPLC), uniformity of dosage units (Ph. Eur.), water content (KF), dissolution (RP-HPLC) and microbial enumeration (Ph. Eur.).

The omission of XRPD analysis for the finished product is justified based on data showing that the desired polymorphic form (form A) does not change when the finished product is stored under accelerated conditions (40 ºC / 75% RH) for 6 months and in an open dish for 24 weeks.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from 56 pilot to production scale batches of the finished product manufactured at the manufacturing sites and using the active substance from active substance manufacturing sites were provided. The results are within the specifications and consistent from batch to batch.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 60 batches including each strength of the finished product and both manufacturers stored for up to 12 months under long term conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative to those proposed for marketing and were packed in primary packaging representative of the ones proposed for marketing. Active substance sourced from the manufacturers was used in different batches of finished product. It is noted that the active substance manufacturing processes at both manufacturers are essentially the same. Therefore, finished product registration batches are considered representative of commercial product produced with active substance.

Finished product may be packaged in either HDPE screw cap bottles or a Aclar / foil blisters. As described in ICH Q1D, Bracketing and Matrixing Designs for Stability Reduced design has been applied in the case of Alunbrig tablets. For 30 mg, 90 mg, and 180 mg tablets packaged in HDPE bottles, there are multiple fill counts for each tablet strength, where the bottle size, closure and inclusion of desiccant remain unchanged. Consequently, a bracketing design for each tablet strength has been used within the registration stability protocols in order to assess the stability profile of multiple packaging configurations, where the high and low tablet fill counts represent the bracketing extremes. A bracketing design was not used for the blister strip packaging configuration (all tablet strengths).

Samples were tested for description (visual), assay (RP-HPLC), degradation products (RP-HPLC), water content (KF), dissolution (Ph. Eur.) and microbial enumeration (Ph. Eur.) The analytical procedures used are stability indicating.

Overall, there were no significant trends or changes in description, assay and dissolution results for the registration lots throughout the duration of testing under long-term and accelerated storage conditions. The description, assay and dissolution results are generally consistent for registration lots (of all strengths) when packaged in bottle and blister configurations. Specified degradant has been observed in 30 mg registration lots at the accelerated and long term storage conditions. Additionally, degradant is also observed in 90 mg and 180 mg registration lots at the accelerated storage conditions. Although reportable levels of the degradant show a slight increase during storage, all degradant results for all registration lots at all conditions are well within the qualified specification limit throughout the duration of testing. Linear regression analyses of the available stability data for all three strengths (i.e. 30 mg, 90 mg, 180 mg) demonstrate that specified degradant will remain within the specified limit for at least 36 months at 30 °C / 75%RH.

In addition, two batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Available photostability results showed no significant change in the description, assay, degradants, water content and dissolution profile of brigatinib tablets, 30 mg and 180 mg. Therefore, the finished product is not considered photosensitive.

An in-use period of 60 days has been proposed for all dosage strengths. Stability data has been provided for 30 mg tablets at the beginning of shelf life. The results demonstrate that all test parameters are well within the specification through 60 days of testing which is beyond the intended use period (1 month patient supply). Based on available data, the in-use period is considered justified.

Based on available stability data, the proposed shelf-life of 36 months with no special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the active substance and the finished product and their manufacturing processes. However, no design spaces were claimed for either.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data have been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

All safety pharmacology in vivo studies as well as the pivotal toxicology studies were conducted in compliance with Good Laboratory Practice (GLP) Regulations.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Four sets of studies were performed to assess the primary pharmacodynamic activities of brigatinib.

A broad in vitro screen was conducted to understand the kinase selectivity profile of brigatinib, and a crystal structure of brigatinib in complex with ALK was determined. In addition, the anti-ALK and anti-ROS1 activities of brigatinib were characterized through a series of in vitro and in vivo studies. These studies included assessment of the mechanism, potency, and specificity of kinase target inhibition by brigatinib. Cell lines used include those derived from NSCLC and anaplastic large cell lymphoma (ALCL), as well as engineered cell lines. Because brigatinib also inhibits certain mutant variants of EGFR, studies were also performed to analyze anti-EGFR activities.

Analysis of the *In vitro* Kinase Profile of Brigatinib and its Primary Metabolite, AP26123 (ARP227)

The in vitro kinase activity screens showed that brigatinib inhibits both wild type ALK and several known ALK mutant variants including G1202R with IC50 values of 0.5 to 4.9 nM.

The metabolite AP26123 inhibited ALK, 4 members of the EGFR family of kinases, IGF-1R, and INSR, with potency similar to, or slightly reduced (by ≤4.5-fold) than that of brigatinib.

Table 4: Brigatinib In Vitro Kinase Activity Against 93 Kinases

IC50 ≤10 nM		IC50≤100 nM		IC50>100 nM			
Kinase	IC50 (nM)	Kinase	IC50 (nM)	Kinase	IC50 (nM)	Kinase	IC50 (nM)
ALK	0.6	RSK3	13	PHKg2	108	PKD2/PRKD2	285
FER	1.3	TYK1 / LTK	14	c-Kit (D816H)	111	c-Src	329
EGFR (L858R)	1.5	YES	19	LOK/STK10	123	BRSK1	338
FLT3 (D835Y)	1.5	RET (V804M)	22	BRSK2	125	FGFR3	358
ROS/ROS1	1.9	CLK1	23	MARK3	127	FMS	358
FLT3	2.1	PYK2//PTK2B/FAK2	24	MARK1	127	SIK2/SNF1KL2/QIK	466
FES/FPS	3.5	RSK2	26	FGFR1	128	FGR	492
FAK/PTK2	3.9	RET (V804L)	27	BLK	136	TAOK1	493
BRK	4.1	ErbB4/HER4	27	TSSK2	138	ABL1	500
STK22D	4.4	CAMKIId	29	Aurora A	146	LCK	512
CHK2 (I157T)	5.6	EGFR (L858R, T790M)	29	JAK2	154	PLK1	611
CHK2	6.5	CHK1	30	INSR	160	BTK	674
		RSK1	30	c-Src (T341M)	165	KDR/VEGFR2	816
		FGFR1 (V561M)	41	ABL1 (Q252H)	171	MELK	895
		RSK4/RPS6KA6	42	FGFR4	181	PKG1a	1012
		ErbB2/HER2	42	c-Kit (V560G)	195	MST1/STK4	1059
		IRR/INSRR	45	PKCnu/PKD1	197	TIE2/TEK	1123
		ARK5	47	FYN	198	NEK9	1146
		CAMKIIg	48	HCK	198	Aurora B	>1000
		LRRK2	51	FGFR2 (N549H)	203	Aurora C	>1000
		FRK/PTK5	52	MLK1/MAP3K9	218	c-MER	>1000
		EGFR (T790M)	56	FGFR2	228	EPHA1	>1000
		FLT4/VEGFR3	58	CLK2	240	EPHA7	>1000
		RET	65	LYN	241	EPHB1	>1000
		EGFR	67	ABL1 (T315I)	242	TRKB/NTRK2	>1000
		IGF-1R	73				
		CAMKK2	82				
		c-Kit (D816V)	83				
		MNK1 (T385D)	88				
		MARK2 / PAR-1Ba	93				
		PKCnu/PKD3	95				

Table 5: Brigatinib In vitro Kinase Activity Against 14 ALK Variants

Kinase	IC50 (nM)	Kinase	IC50 (nM)
ALK-TPM3	1.9	ALK (T1151M)	0.5
ALK-NPM1	4.6	ALK (F1174S)	1.5
		ALK (T1151-L1152insT)	1.5
		ALK (L1152R)	1.7
		ALK (C1156Y)	2.1
		ALK (G1269S)	2.1
		ALK (F1174L)	2.1
		ALK (L1196M)	2.5
		ALK (S1206R)	2.8
		ALK (G1269A)	2.9
		ALK (R1275Q)	4.8
		ALK (G1202R)	4.9

Note: Kinases are listed in order of increasing IC50, with recombinant fusions shown on the left and ALK variants containing secondary resistance mutations shown on the right.

In vitro studies to assess the ALK inhibitory activity of brigatinib using cancer-derived cell lines

Effect of Brigatinib, AP26123, and Crizotinib on Growth of NPM-ALK Positive ALCL Cell Lines (ARP192)

The effect of brigatinib on the growth of 5 NPM-ALK positive ALCL cell lines (KARPAS-299, SU-DHL-1, DEL, L-82, and SUP-M2) and one ALK negative ALCL cell line (U-937) was determined. AP26123, the primary metabolite of brigatinib, and crizotinib, were tested for comparison.

Table 6: Effect of Brigatinib, AP26123, and Crizotinib on Growth of ALK-Positive and ALK-Negative ALCL Cell Lines

Cell Line	ALK Status	Brigatinib GI50 ± SD (nM)	AP26123 GI50 ± SD (nM)	Crizotinib GI50 ± SD (nM)
KARPAS-299	NPM-ALK fusion	10.5 ± 1.5	25.7 ± 4.6	119 ± 22
SU-DHL-1	NPM-ALK fusion	8.8 ± 1.7	20.7 ± 3.8	99 ± 21
DEL	NPM-ALK fusion	30.8 ± 19	41.3 ± 31.5	309 ± 122
L-82	NPM-ALK fusion	10.1 ± 3.2	40.0 ± 17	140 ± 49
SUP-M2	NPM-ALK fusion	15.0 ± 5.1	30.8 ± 8.5	139 ± 3.8
U-937	ALK Negative	2387 ± 400	2540 ± 446	928 ± 155

Effect of Brigatinib and Crizotinib on Signalling in NPM-ALK Positive ALCL Cell Lines (ARP193)

The effect of brigatinib on ALK phosphorylation and signalling downstream of ALK was examined in 5 NPM-ALK positive ALCL cell lines and one ALK negative ALCL cell line. Crizotinib was tested for comparison.

Brigatinib had no effect on signalling in the ALK-negative ALCL cell line.

Table 7: Effect of Brigatinib and Crizotinib on ALK Phosphorylation in ALCL Cell Lines

Cell Line	Brigatinib IC50 ± SD (nM)	Crizotinib IC50 ± SD (nM)
KARPAS-299	3.2 ± 2.8	33 ± 15
SU-DHL-1	1.5 ± 1.3	23 ± 13
DEL	6.6 ± 3.18	ND
L-82	2.1 ± 0.52	ND
SUP-M2	12 ± 11.95	ND

ND: Not determined

Effect of Brigatinib and Crizotinib on Growth of EML4-ALK Positive NSCLC Cell Lines (ARP194)

Brigatinib and crizotinib inhibited the anchorage-independent growth of H2228 cells with IC50s of 2.4 and 86.7 nM, respectively.

Table 8: Effect of Brigatinib and Crizotinib on Growth of ALK-Positive and ALK-Negative NSCLC Cell Lines

Cell Line	ALK Status	Brigatinib GI50 ± SD (nM)	Crizotinib GI50 ± SD (nM)
H3122	EML4-ALK fusion	4.2 ± 1.2	61.5 ± 18.2
H2228	EML4-ALK fusion	10.1 ± 6.8	121 ± 61
H23	ALK Negative	1337 ± 875	1773 ± 743
H838	ALK Negative	503 ± 400	1307 ± 270

Effect of Brigatinib and Crizotinib on Signalling in EML4-ALK Positive NSCLC Cell Lines (ARP195)

The effect of brigatinib on ALK phosphorylation and/or signalling downstream of ALK was examined in 2 EML4-ALK positive (H3122 and H2228) and 1 ALK-negative (H23) NSCLC cell line.

The inhibition of ALK by brigatinib and crizotinib was accompanied by a substantial inhibition of ERK, AKT, STAT3, and S6 phosphorylation in ALK-positive cell lines. Brigatinib had no effect on signalling in an ALK-negative NSCLC cell line (H23).

Table 9: Effect of Brigatinib and Crizotinib on ALK Phosphorylation in NSCLC Cell Lines

Cell line	Brigatinib IC50 ± SD (nM)	Crizotinib IC50 ± SD (nM)
H3122	3.7 ± 1.6	43 ± 37
H2228	4.5 ± 2.2	55 ± 4.0

***In vivo* studies to assess the ALK inhibitory activity of brigatinib using cancer-derived cell lines**

Oral Efficacy Study of Brigatinib and Crizotinib in a Subcutaneous Xenograft Model Using the KARPAS-299 Human ALCL Cell Line (ARP614)

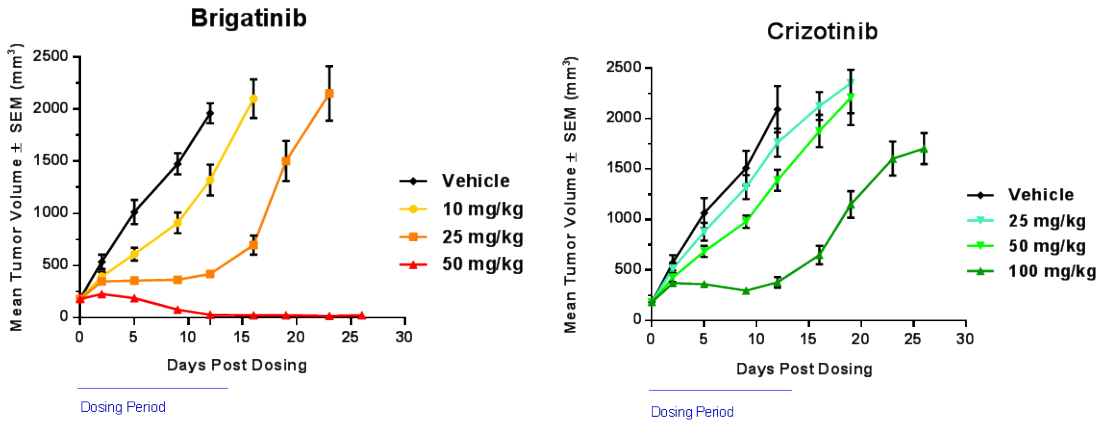


Figure 2: **Effect of Brigatinib and Crizotinib on Tumour Growth in a KARPAS-299 ALK-positive ALCL Xenograft Model**

Multi-Dose PK/PD Study of Brigatinib and Crizotinib in a Subcutaneous Xenograft Model Using the KARPAS-299 Human ALCL Cell Line (ARP615)

The highest levels of brigatinib detected, all at 2 h, were 579, 1829, and 2731 ng/mL and AUCs were 3039, 11827, and 26211 hr.ng/mL for the 10, 25, and 50 mg/kg doses, respectively. Compared to vehicle-treated mice, greater than 90% inhibition of p-ALK was observed in tumours at the 2 and 10 h time points for all 3 brigatinib dose levels. At 24 h, p-ALK levels were inhibited by 60%, 83%, and 90%, in the 10, 25, and 50 mg/kg dose groups, respectively. Plasma concentrations of crizotinib at 25 and 50 mg/kg (2 h and AUC) were comparable to concentrations of brigatinib at the same doses (e.g levels at 2 h were 2000, and 4049 ng/mL, respectively); however the degree of p-ALK inhibition in the tumour was less than that observed with brigatinib (eg, 11% and 31% at 24 h). In general, including analysis of mice treated with 100 mg/kg crizotinib, plasma levels of crizotinib that were at least 3-8-fold greater than brigatinib were required to achieve a similar level of p-ALK inhibition in the tumour.

Oral Efficacy Study of Brigatinib in a Subcutaneous Xenograft Model Using the H3122 Human NSCLC Cell Line (ARP202)

Brigatinib induced a dose-dependent inhibition of tumour growth, with significant tumour regression ($p < 0.01$) achieved at all dose levels. Relative to the tumour size before treatment, tumour size was reduced by 36% at the 10 mg/kg dose level and by >90% at the 25, 50, and 75 mg/kg dose levels. Tumour regression was maintained for at least 60 days after treatment ended in the 25 mg/kg, and higher, dose groups. All dose levels used in this study were well tolerated with no clinical signs or drug related mortality at any dose level.

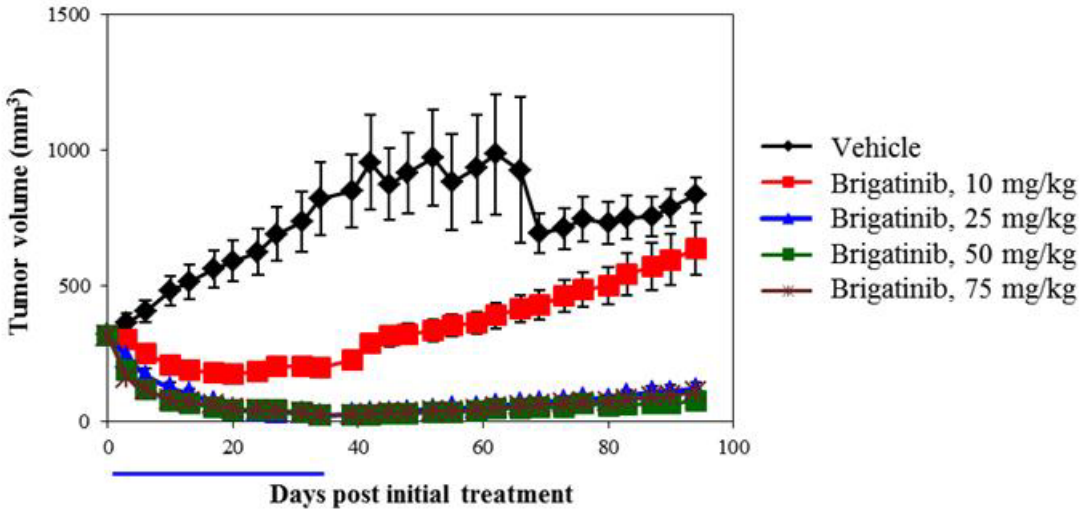


Figure 3: Effect of Brigatinib on Tumour Growth in an H3122 ALK-positive NSCLC Xenograft Model

Single Dose PK/PD Study of Brigatinib in a Subcutaneous Xenograft Model Using the H3122 Human NSCLC Cell Line (ARP199)

The highest levels of brigatinib were detected 2 h post dosing. A concomitant decrease in phosphorylation of signalling proteins downstream of ALK, including ERK, AKT, STAT3, and S6, was also observed.

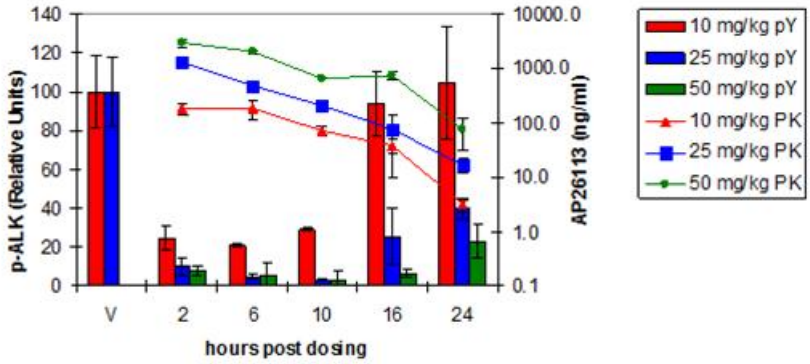


Figure 4: PK and PD Activity of Brigatinib in an H3122 NSCLC Xenograft Model

Oral Efficacy Study of Brigatinib and Crizotinib in a Subcutaneous Xenograft Model Using the H2228 Human NSCLC Cell Line (ARP616)

A dose-dependent effect of brigatinib on tumour growth was observed, with statistically significant regression ($p<0.001$) achieved at all dose levels. Relative to vehicle treated mice, brigatinib induced tumour regression by 66%, 82%, 85%, and 89% at the 5, 10, 25, and 50 mg/kg dose levels, respectively.

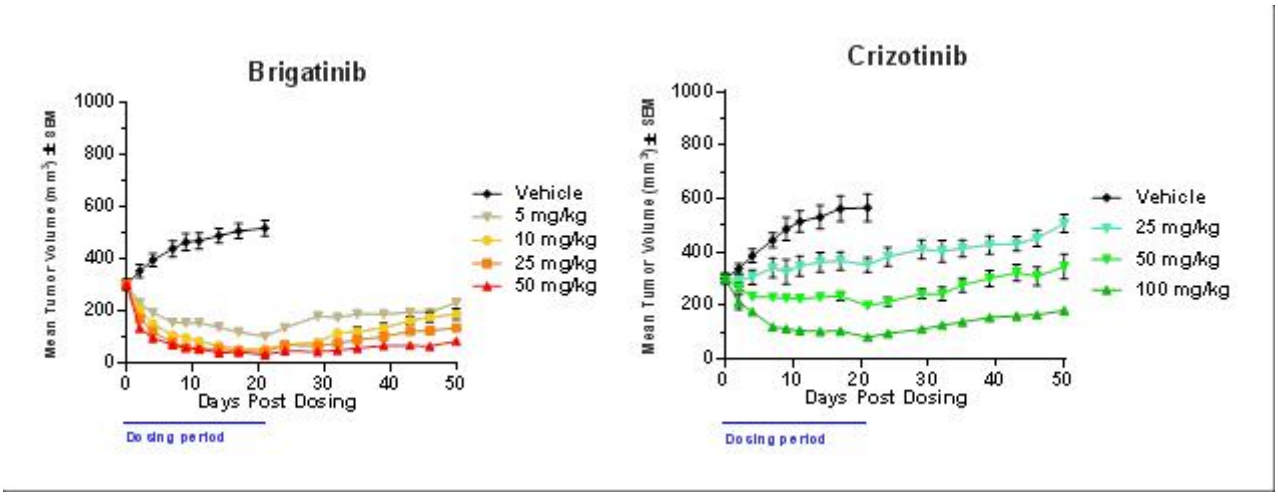


Figure 5: Effect of Brigatinib and Crizotinib on Tumour Growth in an H2228 ALKpositive NSCLC Xenograft Model

Oral efficacy study of Brigatinib, Compared to Crizotinib, in an Orthotopic Brain Tumour Model using the H2228 Human NSCLC Cell Line (ARP621)

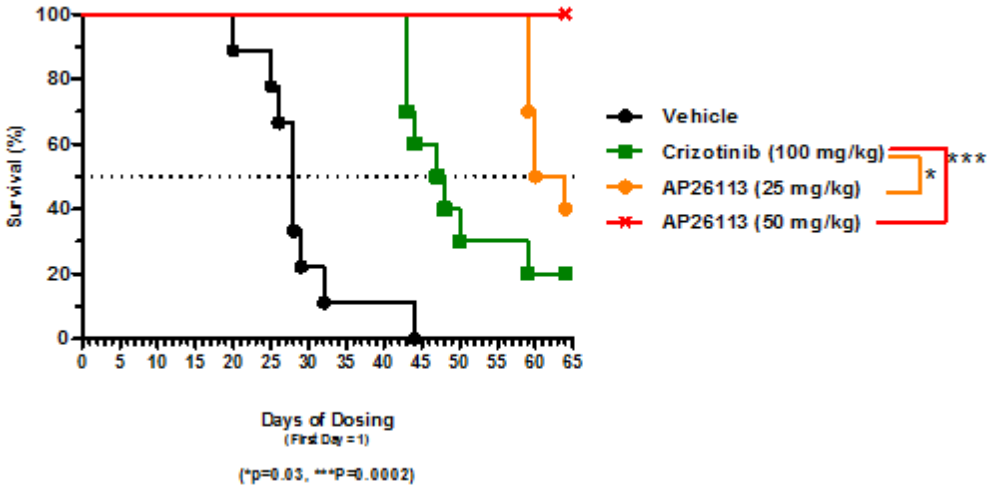


Figure 6: Effect of Brigatinib and Crizotinib on Survival of Mice with ALK-positive NSCLC Tumours Implanted Intracranially

In vitro Identification of Secondary Mutations in ALK that Confer Resistance to Crizotinib, Ceritinib, Alectinib, or Brigatinib (ARP617)

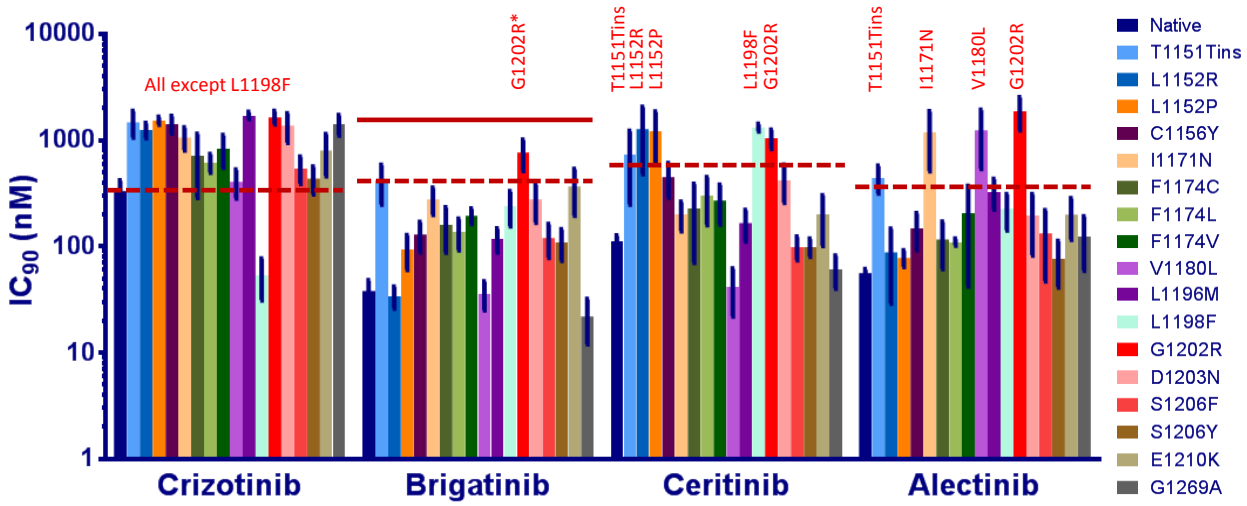
Under the conditions of this *in vitro* assay, no single secondary mutation in ALK was identified that could survive exposure to 500 nM brigatinib.

Table 10: Secondary Mutations in ALK that Confer Resistance to Crizotinib, Ceritinib, Alectinib, or Brigatinib, Identified in an In Vitro Screen

TK1	Concentration (nM)	ALK mutations detected
Crizotinib	500	I1171T/S, F1174C/I/L, S1206A, T1151K, L1196M, F1245C, G1269A
	750	I1171T/N, F1174V/C, C1156Y, L1196M
	1000	L1196M
	1500	None
Ceritinib	100	S1206A, F1174C/V, T1151K, C1156Y, L1198F
	200	F1174C/V/I, S1206A, L1198F
	500	L1198F
	1000	None
	1500	None
Alectinib	100	I1171S/T/N, F1174V
	200	I1171N/S/T, L1196M
	500	I1171N/S, V1180L, L1196M
	1000	I1171N
	1500	None
Brigatinib	100	S1206A, F1174C/V/I/L, I1171N, E1210K
	200	F1174V/C/I, S1206A, E1210K, L1196M
	500	None
	1000	None
	1500	None

Effect of Brigatinib on Viability of Ba/F3 cells Expressing Native EML4-ALK, and 17 Resistance Mutants, Compared to Crizotinib, Ceritinib and Alectinib (ARP618)

A panel of Ba/F3 cell lines was engineered so their viability was dependent on activity of a native EML4-ALK fusion, or 17 variants with secondary mutations in the ALK kinase domain that have been associated with clinical or nonclinical resistance to crizotinib, ceritinib, and/or alectinib. Brigatinib was found to potently (IC50 <200 nM), and selectively (>15-fold selectivity over ALK-negative cells), inhibit viability of all 17 ALK variants. These include the mutations most commonly associated with clinical resistance to crizotinib (L1196M and G1269A) and the only mutation thus far associated with clinical resistance to all three approved ALK inhibitors (G1202R).



Note: Horizontal lines represent the "effective" C_{max} concentrations achieved in patients (for brigatinib, dotted line for 90 mg and solid line for 180 mg). ALK variants with IC90s that exceed the effective C_{max} are indicted in red above the graph. *The IC90 for G1202R exceeds the effective C_{max} for 90 mg, but not 180 mg, brigatinib.

Figure 7: Relationship Between IC90 Values and "Effective" Cmax Plasma TKI Concentrations (ie, Corrected for the Functional Effects of Protein Binding)

In addition, in an in vitro mutagenesis screen, no ALK mutation was identified that could confer resistance to 500 nM brigatinib, a concentration that is clinically achievable.

Oral Efficacy Study of Brigatinib and Crizotinib in Subcutaneous Tumour Models Using Ba/F3 Cell Lines Expressing Native or Mutant EML4-ALK Proteins (ARP215)

Table 11: Effect of Brigatinib and Crizotinib on Tumour Growth in Ba/F3 Native and Mutant (L1196M, G1269S, and S1202R) EML4-ALK Tumour Models

TKI	Mouse Dose (qd) mg/kg	Antitumour Activity (%)*			
		Native EML4-ALK	L1196M EML4-ALK	G1269S EML4-ALK	S1206R EML4-ALK
Brigatinib	10	22	ND	ND	ND
	25	-100	52	-29	0
	50	-100	-59	-98	29
	75	-100	-98	-100	77
Crizotinib	25	1	ND	ND	ND
	50	0	ND	ND	ND
	100	25	15	4	0
	200	-100	12	0	7

*Percent tumour growth inhibition is indicated in black and percent tumour regression (negative value) is indicated in red. ND, not determined

Single Dose PK/PD Study of Brigatinib and Crizotinib in Subcutaneous Tumour Models Using Ba/F3 Cell Lines Expressing Native or Mutant EML4-ALK Proteins (ARP229)

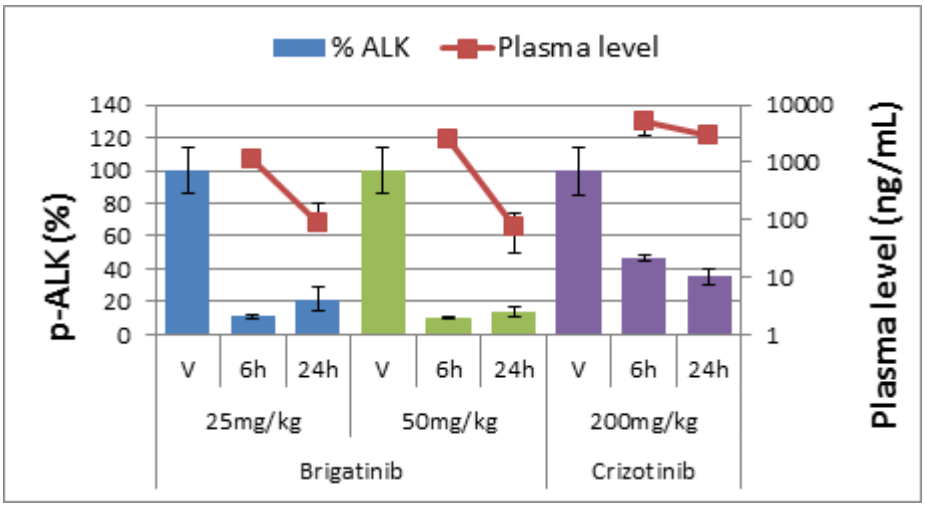


Figure 8: PK and PD Activity of Brigatinib and Crizotinib in a Ba/F3 Native EML4-ALK Tumour Model

Oral Efficacy Study of Brigatinib in Ba/F3 EML4-ALK Native and G1202R Mutant Tumour Models, Compared to Other ALK Inhibitors (ARP619)

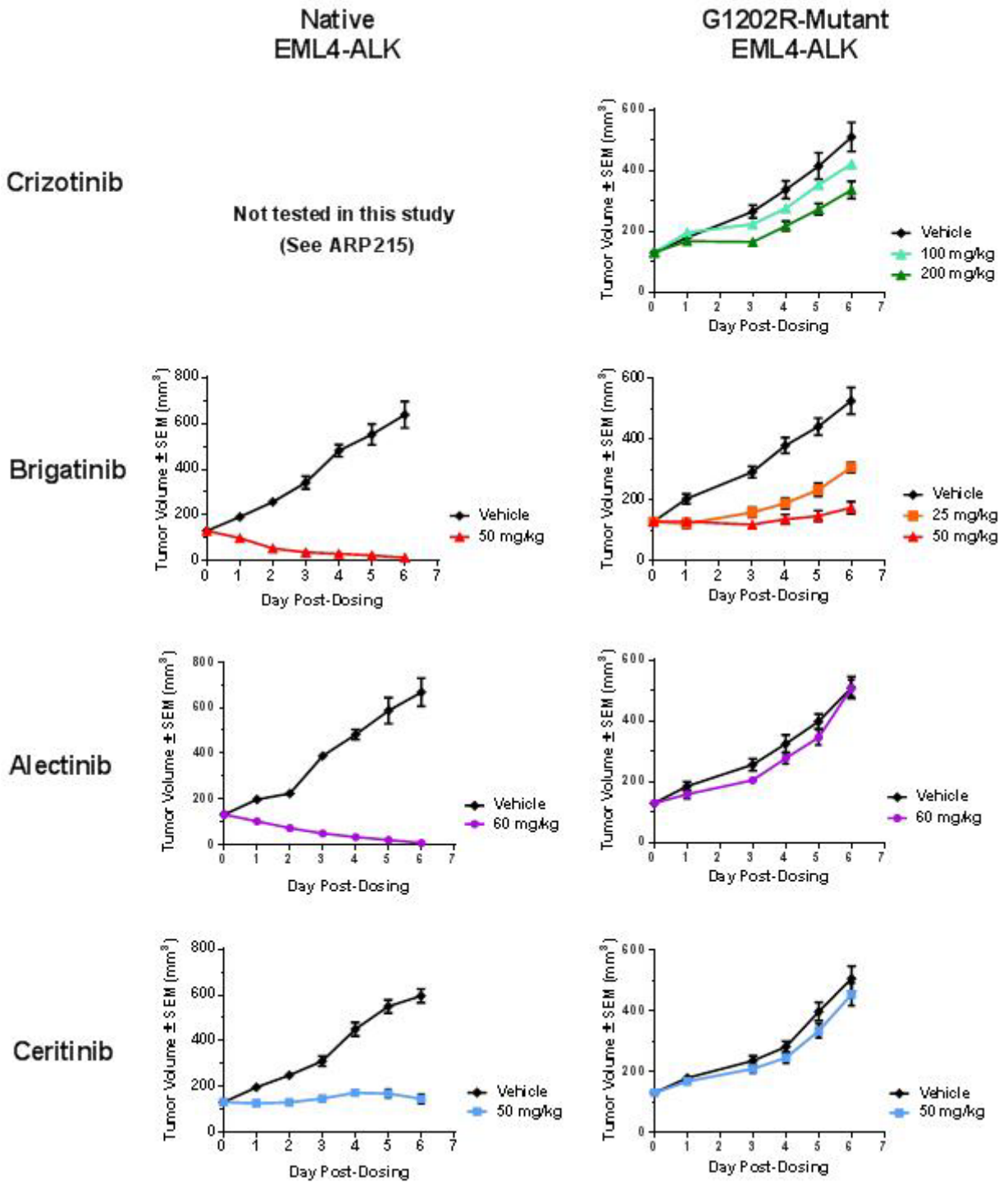


Figure 9: Effect of Brigatinib and Other ALK Inhibitors on Tumour Growth in Ba/F3 Native and G1202R Mutant EML4-ALK Tumour Models

Single Dose PK/PD Study of Brigatinib in Ba/F3 EML4-ALK Native and G1202R Mutant Tumour Models, Compared to Other ALK Inhibitors (ARP620)

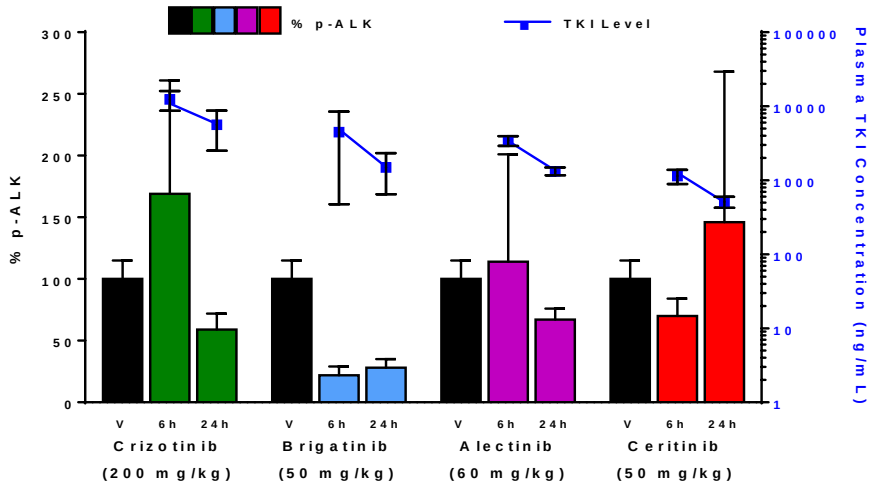


Figure 10: PK and PD Activity of Brigatinib and Other ALK Inhibitors in a Ba/F3 G1202R Mutant EML4-ALK Tumour Model

ROS1 Inhibitory Activity of Brigatinib

In cellular and in vivo assays such as the Effect of Brigatinib on Signalling and Viability of Ba/F3 Cell Lines Expressing ROS1 Fusions (ARP622) and Oral Efficacy Study of Brigatinib in a Ba/F3 CD74-ROS1 Subcutaneous Tumour Model (ARP623), brigatinib inhibited ROS1 with potency similar to that of ALK. Brigatinib inhibited viability of Ba/F3 cells expressing ROS1 fusions observed in NSCLC patients with IC50s of 16-31 nM. Once daily oral administration of 50 mg/kg brigatinib induced tumour regression in mice implanted with such tumours.

EGFR Inhibitory Activity of Brigatinib

In cellular and in vivo assays, brigatinib exhibited varying levels of activity against mutant variants of EGFR.

The variant that was most sensitive to brigatinib was EGFR-Del, which contains a deletion in exon 19 and is one of the two most common activated EGFR variants in NSCLC patients. Brigatinib inhibited the viability of Ba/F3 cells expressing EGFR-Del (ARIAD Report ARP624) with an IC50 of 95 nM and once daily oral administration of 25 mg/kg brigatinib induced tumour regression in mice implanted with a NSCLC cell line expressing EGFR-Del (ARIAD Report ARP216). In contrast, brigatinib inhibited EGFR-L858R (the second most common activated variant), and variants containing an activating mutation and a T790M resistance mutation, less potently in cellular assays (IC50s 272 - 489 nM). In ARIAD Report ARP205, the IC90s for inhibition of variants containing a T790M resistance mutation (IC90s 2461-2968 nM) were greater than the IC90s for variants containing activating mutations alone, especially EGFR-Del (IC90 314 nM). Consistent with these Reports ARP219 and ARP625, once daily oral administration of 50 mg/kg brigatinib to mice did not significantly inhibit growth of a patient-derived tumour containing EGFRL858R/ T790M. Brigatinib did not inhibit native EGFR activity in a cellular assay (IC50 >3000 nM).

Secondary pharmacodynamic studies

In secondary pharmacology studies brigatinib exhibited minimal off-target activity against a panel of targets, indicating lack of promiscuity for binding to non-specific pharmacological effectors. In the presence of 10 µM brigatinib, only 2/62 targets (3%) were inhibited by ≥50% (sigma receptor [non-selective] and sodium ion channel [site 2]). In comparison, 10 µM crizotinib inhibited 11 targets (18%) by ≥50% (including sigma receptor and sodium ion channel) (ARP630).

Safety pharmacology programme

Brigatinib plasma concentration multiples are reported relative to the human steady state GeoMean Cmax of 1452 ng/mL (2485 nM) at the 180 mg QD dose of brigatinib (hereafter referred to as "the human Cmax").

In vitro hERG study (Report No. AA778105 non-GLP): Brigatinib was tested in a non-GLP hERG assay to determine the potential to impair cardiac repolarization. The IC50 in this study was determined to be >10µM which is well above the human Cmax concentration (2458 nM).

Cardiopulmonary Assessment in Radiotelemetry Instrumented Cynomolgus Monkeys (69507 GLP): Administration of brigatinib resulted in acute effects of small decreases in heart rate (8 to 10%) at all dose levels and pulse pressure (8 to 9%) at 20 and 30 mg/kg from 1 to 6 hours post-dose. There were also brigatinib-related delayed effects (generally manifesting 32-42 hours post-dose) that resulted in higher heart rate (20 and 30 mg/kg), systolic blood pressure (10, 20, and 30 mg/kg), diastolic blood pressure (30 mg/kg), mean arterial blood pressure (30 mg/kg), and body temperature (30 mg/kg). Delayed respiratory effects (manifesting 19-42 hours post-dose) included increased respiratory frequency at 20 and 30 mg/kg. Brigatinib administration did not result in any changes in ECG waveform morphology, ECG intervals (PR, QRS, QT or QTcB), or minute volume.

Neurofunctional safety pharmacology study in rats (6900915): There were no brigatinib-related CNS effects noted. The NOEL was 100 mg/kg.

Renal System (6900893): The lowest dose of 25 mg/kg administered to the male Sprague-Dawley rat resulted in moderate increases in urea nitrogen and creatinine in the blood. Doses of 50 and 100 mg/kg resulted in an increase in urea nitrogen, creatinine, and glucose, and a decrease in triglycerides and phosphate in the blood, as well as an increase in creatine kinase in the blood. Additionally, increased urinary phosphorus fractional excretion and decreased urine creatinine were noted at 50 and 100 mg/kg, and increased fractional urinary sodium excretion was noted at 100 mg/kg. The NOEL was 25 mg/kg.

Pharmacodynamic drug interactions

No pharmacodynamics drug interaction studies were performed.

2.3.3. Pharmacokinetics

Table 12: Studies Conducted to Determine the ADME Characteristics of Brigatinib

Report Number	Study Objective	Test System	Brigatinib Concentration (or) Target Dose and Route
In vitro			
13ARIAP1R2	Permeability Assessment, Evaluation of the Substrate and Inhibition Potential of Brigatinib for Efflux and Uptake Transporters	C2BBe1, MDR1-MDCK, BCRP-MDCK and MDCK cells, Transporter-Transfected and Vector Control-Transfected HEK Cells, Transfected Vesicles	0.1–120 µM
ARP210	*In vitro* Plasma Protein Binding and Equilibrium Blood/Plasma Partitioning of Brigatinib in Mouse, Rat, Monkey and Human	Mouse, Rat, Monkey, Human Plasma	0.2–5 µM
		Mouse, Rat, Monkey, Human Plasma and Whole Blood	0.1–3 µM
ARP213	*In vitro* Metabolism of Brigatinib in Liver Microsomes, Hepatocytes, and Recombinant Human CYP Isozymes	Rat, Monkey, Human Liver Microsomes and Hepatocytes, Recombinant Human CYP Isozymes	0.1–200 µM
ARP608	*In vitro* Biotransformation of [^{14}C]Brigatinib in Liver Microsomes and Hepatocytes of Mouse, Rat, Monkey and Human, and Recombinant Human CYP Isozymes	Rat, Monkey, Human Liver Microsomes and Hepatocytes, Recombinant Human CYP Isozymes	3, 30 µM [^{14}C]Brigatinib
ARP212	*In vitro* Evaluation of Brigatinib as an Inhibitor of Human Cytochrome P450 Enzymes	Human Liver Microsomes	0.1–100 µM
XT123144	*In vitro* Evaluation of Brigatinib as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes	Human Hepatocytes	0.25–20 µM
In vivo			
ARP208	Pharmacokinetics of Brigatinib in Female CD-1 Mice and in Male Sprague-Dawley Rats Following Oral Administration	Female CD-1Mice	10, 50 mg/kg; PO
		Male Sprague-Dawley (SD) Rats	2 mg/kg; IV 10 mg/kg; PO
ARP209	Pharmacokinetics of Brigatinib in Cynomolgus Monkey following Administration of an Intravenous Dose, an Oral Solution Dose and an Oral Dose	Male Cynomolgus Monkeys	5 mg/kg; IV 15 mg/kg; PO Solution 15 mg/kg: PO Drug
ARP609	Pharmacokinetics, Metabolism and Excretion of [^{14}C]Brigatinib Following Oral Administration to Intact and Bile Duct-Cannulated Rats	Male SD Rats	30 mg/kg [^{14}C]Brigatinib (200 µCi/kg); PO
280N-1201	Quantitative Tissue Distribution of Drug-Related Material Using Whole-Body Autoradiography Following a Single 30 mg/kg Oral Dose of [^{14}C]Brigatinib to Male Long-Evans and Albino Sprague-Dawley Rats and Human Radiation Dosimetry Prediction	Male Albino SD and Pigmented Long-Evans (LE) Rats	30 mg/kg [^{14}C]Brigatinib (225 µCi/kg); PO
ARP610	Pharmacokinetics, Metabolism and Excretion of [^{14}C]Brigatinib Following Oral Administration to Monkeys	Male Cynomolgus Monkeys	30 mg/kg [^{14}C]Brigatinib (40 µCi/kg); PO
ARP611	Pharmacokinetics, Metabolism and Excretion of [^{14}C]Brigatinib Following Oral Administration to Healthy Male Subjects	Humans	180 mg (100 µCi); PO

Absorption:

In vitro Permeability, P-gp, and BCRP Substrate Assessment of Brigatinib: Brigatinib was found to be a substrate of both P-gp and BCRP.

Single Dose Pharmacokinetic Studies of Brigatinib in Multiple Species

Brigatinib was well-absorbed from the gastrointestinal tract despite being an efflux substrate. The oral bioavailability in rat and monkey was approximately 40% to 53%. Brigatinib was of low clearance in rat and monkey, with a moderate volume of distribution, and moderate-to long elimination half-life. *In*

vitro, brigatinib was moderately bound (64.1% to 73.0%) to mouse, rat, monkey, and human plasma proteins. Brigatinib did not show preferential distribution into red blood cells over plasma in mouse, rat, monkey, and human blood.

Table 13: Pharmacokinetic parameters of brigatinib in mice, rats, and monkeys

	Dose (mg/kg)	Route	Cmax ()	Tmax (h)	AUC_{last} (h·ng/mL)	$AUC_{0-\infty}$ (h·ng/mL)	t½, el ()	CL	V_z (mL/kg)	F (%)
Mouse Brigatinib										
	10	PO	768	1	5533	5579	3.5	-	-	-
	50	PO	3530	1	32482	32624	3.3	-	-	-
Rat Brigatinib										
	2	IV	-	-	4329 ± 302	4400 ± 296	4.4 ± 0.4	460 ± 31	2925 ± 465	-
	10	PO	977 ± 92	3.3 ± 1.2	8757 ± 833	8936 ± 833	4.0 ± 0.6	-	-	40.7
Cynomolgus Monkey Brigatinib										
	5	IV	-	-	11137 ± 1551	11203 ± 1550	7.70 ± 0.5	452 ± 63	3257 ± 994	-
	15	PO solution	1757 ± 524	4.0 ± 0.0	17535 ± 1729	17706 ± 1779	6.95 ± 0.415	-	-	52.9 ± 3.3
	15	PO	1453 ± 172	3.0 ± 1.0	15193 ± 615	15343 ± 645	7.24 ± 0.12	-	-	46.4 ± 8.3
Cynomolgus monkey AP26123-										
	5	IV	-	-	513 ± 42	542 ± 55	6.28 ± 1.32	-	-	-
	15	PO solution	264 ± 28	3.0 ± 1.0	2351 ± 179	2384 ± 179	7.63 ± 1.04	-	-	-
	15	PO	224 ± 19	3.0 ± 1.0	2034 ± 168	2065 ± 171	8.52 ± 0.79	-	-	-

Abbreviations: -- = Not applicable; AUC_{last} = Area under the plasma concentration-time curve from time 0 to time of last measurable concentration above the lower limit of quantitation; $AUC_{0-\infty}$ = Area under the plasma concentration-time curve from time 0 to infinite time; CL = Clearance; C_{max} = Maximum observed plasma concentration; T_{max} = Time to reach C_{max}; $t_{1/2}$ = Half-life; V_z = Volume of distribution
a: Solution in 25 mM citrate buffer (pH 4.0)
b: Drug (brigatinib)
c: $AUC_{0-\infty}$ Ratio calculated as $AUC_{0-\infty,}$ AP26123/$AUC_{0-\infty,}$ Brigatinib
d: Calculated as (Dose, iv/Dose, po)*($AUC_{0-\infty,\ po}$/$AUC_{0-\infty,\ iv}$)
Note: Values in the table represent the mean or mean ± SD of n=3 animals

Distribution:

[14C]brigatinib-derived radioactivity was widely distributed to tissues of albino and pigmented rats reaching Cmax in most tissues at or before 4 h post-dose in albino rats and at or before 24 h post-dose in pigmented rats, and declined thereafter. The tissues of albino and pigmented rats with the highest relative tissue concentrations (range: 51.942 to 253.475 µg-equiv/g) were small intestine, thyroid, liver, stomach, Harderian gland, pituitary gland, kidney cortex, spleen, adrenal gland medulla, and pigmented eye uvea. High concentrations were also present in the alimentary canal contents, bile, and urine, which demonstrated that both renal and biliary excretion were routes of elimination of brigatinib. Tissues with the lowest concentrations (<2.0 µg-equiv/g) in albino and pigmented rats included the central nervous system, eye lens, white adipose, and bone. Although C_{max} in the uvea of the eye of the pigmented rats was higher (177.806 µg-equiv/g at 24 h) than that observed in albino rats (C_{max} of 7.545 µg-equiv/g at 0.5 h), the concentrations of radioactivity in the eye uvea of pigmented rats showed a steady but slow decline from 24 to 672 h post-dose. Drug-related radioactivity was detected in the brain of Sprague Dawley rats with a combined area under the concentration-time curve from time 0 to infinity (AUC∞) of 5.73 µg-eq*hr/g across the cerebellum, cerebrum, and medulla. In addition, drug-related radioactivity was measurable in the spinal cord with an AUC∞ of 5.11 µg-eq*hr/g.

Metabolism

The *in vitro* metabolite profiles in rat, monkey, and human liver microsomes and hepatocytes were qualitatively similar. All *in vitro* metabolites of brigatinib in human liver microsomes and hepatocytes were also observed in mouse, rat or monkey liver microsomes and/or hepatocytes. The primary metabolic pathway of brigatinib in liver microsomes across all species tested and in human hepatocytes was N-demethylation to form M36 (N-desmethyl brigatinib; AP26123). The major metabolite in mouse, rat and monkey hepatocytes was M21 (brigatinib GSH conjugate), while M36 (AP26123) was the second most abundant metabolite in rat and monkey hepatocytes. In rat and monkey hepatocytes the minor metabolites included M4 and M21a (brigatinib GSH conjugates), M5 (hydroxy-brigatinib-ene GSH conjugate), M22 (brigatinib N-oxide; AP32831); M25 (brigatinib N-oxide; AP32830), and M13 (monooxy-brigatinib glucuronide).

In vivo, following oral administration of [14C]brigatinib to rats, monkeys, and humans, metabolite profiles were qualitatively similar with no unique human metabolites observed. N-demethylation was the primary biotransformation pathway of brigatinib leading to the formation of M36 (N-desmethyl brigatinib; AP26123). The parent drug, brigatinib, was the major circulating radioactive component accounting for approximately 75-92% of total radioactivity (TRA) in plasma accompanied by <10% of M36 (AP26123). In humans, the oxidative metabolite M36 (AP26123) accounted for 3.5% of the total circulating radioactivity and <10% of parent AUC.

Elimination

The predominant route of elimination of brigatinib in rats, monkeys, and humans was fecal excretion, although in humans renal excretion also contributed to drug elimination (Report No. ARP609, ARP610, and ARP611). Excretion of radioactivity was essentially complete in all species. Unchanged brigatinib accounted for 55.74%, 14.58%, and 26.49% of the radioactive dose in rat, monkey, and human feces, respectively. In urine, unchanged brigatinib accounted for 5.18%, 5.02%, and 21.38% of the radioactive dose in rat, monkey, and human urine, respectively and 2.89% of the radioactive dose in rat bile.

Pharmacokinetic drug interactions

In vitro studies indicated that CYP2C8 and CYP3A4 are the major isozymes responsible for brigatinib metabolism, with minor contribution from CYP3A5. *In vitro*, brigatinib and its metabolite, AP26123, did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5 at clinically relevant drug concentrations. IC50 values for reversible inhibition of CYPs by brigatinib and AP26123 were >100 µM; the only exception was the IC50 of 72.9 µM (brigatinib) and 63.8 µM (AP26123) for inhibition of midazolam 1'-hydroxylation mediated by CYP3A4/5. The Ki values (IC50/2) for brigatinib and AP26123 are 36.5 µM and 31.9 µM, respectively.

2.3.4. Toxicology

Two species were selected based on *in vitro* metabolism data. The cynomolgus monkey has also been used to study toxicology in line with other ALK TKIs.

Single dose toxicity

Study ID	Species/ Sex/Number/ Group	Dose/Route	Approx. lethal dose / observed max non-lethal dose	Major findings
ARP223	Mouse 5M/F	Oral 0, 50, 75, 125, 250, 400 mg/kg	75 mg/kg	Decreased activity, prostration, decreased body weight, Lethality ≥125 mg/kg (4/10, 9/10 and 10/10)
ARP224	Rat 5 M/F	Oral 0, 50, 75, 125, 250, 400 mg/kg	125 mg/kg	Decreased activity, lethargy, prostration, ruffled fur, squint eye, body weight loss, Lethality ≥250 mg/kg (9/10 and 10/10)

Repeat dose toxicity

Study ID	Species/ Sex/ Number/ Group	Dose(mg/kg) Route	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
Rat					
ARP222 Non-GLP	5 F Sprague Dawley	0, 3, 10, 30, 100 PO	14 day	10 mg/kg/day $C_{max(Day\ 14)}$ 2587 ng/mL $AUC_{(0\text{-}4,\ day\ 14)}$ 41120 h*ng/mL	≥**10 mg/kg:** Decreased WBC, LYMP, EOS Increased blood insulin ≥**30 mg/kg:** body weight loss, Decreased PLT Increased ALT, AST, ALP, BUN Necropsy; small thymus and spleen **100 mg/kg:** mortality Necropsy; full stomach, small thymus, spleen, ovary and uterus

805018 GLP	15 M/F Sprague Dawley	0,15, 30, 60 PO	28 day	15 mg/kg/day AP26113 'C_{max} 1482 ng/mL and $AUC_{(0-24)}$ 22633 h•ng/mL, on Day 28	≥**15 mg/kg:** transient increase in WBC Transient decrease in; %lymp, PLT, retic Increased serum insulin Necropsy: Decreased spleen weight, thymus weight ≥**30 mg/kg:** mortality (4 animals, only 2 (4%) AP26113 related) decreased activity, thinness, abdominal distension, dehydration, weakness, partially closed eyes, reduced body temperature, and hunched posture, reduced food consumption Increased AST, ALT, serum Glucose, CHOL (M), Necropsy; decreased weight of prostate and uterus (correlated to atrophy microscopically), spleen weight (correlated to atrophy/necrosis af the red and white pulp), thymus weight (correlated to lymphoid atrophy) F: dark digestive content, likely corresponding to blood from microscopic stomach erosions/ulcers M: small prostate and seminal vesicles (correlated to minimal to moderate atrophy) Femur; osteoblast necrosis. **60 mg/kg/day:** Dosing stopped on Day 5 (M) and 6 (F) Clinical signs as above and; tremors, firm abdominal inter-structure, emaciation, moribundity, and mortality (58%) One or more animals euthanized showed increased; AST, ALT, ALP, GGT, urea, creatinine, and glucose Dark digestive content in both sexes (see above) Dark adrenals (correlated to slight haemorrhage), dark harderian glands (pigment deposition)

69505 GLP	25 m/F Sprague Dawley	0, 7.5, 15, 25 PO	6 month	**No NOAEL** STD10 7.5 mg/kg/day AP26113 C_{max} 1150 ng/mL and $AUC_{(0-24)}$ 18600 h•ng/mL, on Day 182	Mortality in all groups, 1, 3, 9 and 6 animals per group respectively. The control group animal as well as the three 3 7,5 mg/kg and one 25 mg/kg animals were deemed incidental and due to gavage error. The remaining mortalities in the mid and high dose groups were due to AP26113 treatment, acute cardiac lesions, cardiomyopathy and chronic renal tubular degeneration was found to be the causes. ≥ **7,5 mg/kg:** clinical signs; pale and/or cool body and extremities, dermal atonia, thin appearance, convulsions, increased respiration rate, decreased defecation, dried brown material around the anogenital area, dried red material around the nose and mouth, labored respiration, shallow respiration, and red urine. Cleared during the recovery period ≤15 mg/kg, but persisted in the 25 mg/kg group. Reduced body weight, reduced food consumption. Increased FIB, WBC, LYM, EOS Increased ALP, ALT, AST, SDH, CHOL, Ca, UREA, CREAT, P, TP, GLUC Decreased K, Cl Urine: higher K and Cl, proteinuria (correlated to protein casts present) *Opthalmoscopic findings*: Week 25: bilateral cataracts 1 M (7,5 mg), 3 M (15 mg), bilateral retinal degeneration 3F (15 mg). Week 33: bilateral cataract 1 M + 2F (7.5 mg), 4 M + 1 F (15 mg), bilateral retinal degeneration 1 F (15 mg) Necropsy: *dark red discoloration of the kidneys, soft and small testes, and small thymus* lower organ weights; spleen, thmus, pituitary gland, *testes*, seminal vesicles/prostate, *epididymides* Microscopic findings: renal changes, hepatocellular necrosis,pancreas; acinar atrophy and islet fibroplasia, reduced cellularity in spleen, thymus, axillary and mesenteric lymph nodes, testicular tubular degeneration, **15 mg/kg:** Reduced MCHC (F) Increased NEU (M) Increased bili (F) Urine higher Na (F) ≥**15 mg/kg:** Decreased RBC, HB, HT, Increased MCV, RBW, HBW, PLT Increased GGT Urine: higher volume, decreased specific gravity Microscopic findings: Myocardial degeneration **25 mg/kg:** Treatment stopped on Day 53. Remaining 8M and 6F euthanized following a 56 day recovery period. Urine: low pH, pos gluc
Cynomolgus monkey					

QAA00205 Non-GLP	1 M/F	0, 3, 10, 30 PO	14 day	NOAEL 10 mg/kg/day	All animals (incl control): Mild foamy macrophages (histiocytosis) in the lungs ≥**3 mg**: Increased serum insulin (M) Decreased thymus weights, spleen weights. **30 mg:** decreased LYMP Decreased thymus weight (moderate lymphoid depletion) Slight increased ALT Increased serum insulin and glucose (F)
80502 GLP	5 M/F	0, 7.5, 15, 45 PO	28 day	7.5 mg/kg/day AP26113 C_{max} 543 ng/mL and $AUC_{(0-24)}$ 3383 h•ng/mL, On Day 28	Mortality (4 M + 1 F) observed at 45 mg/kg. Dosing stopped on Day 8/7. Gastrointestinal toxicity established as cause. ≥**15 mg:** Decreased activity, soft/liquid stools. Increased ALT, AST Increased serum insulin, gluc Decreased P Microscopy: lymphoid atrophy/necrosis in the thymus, spleen, mesenteric and mandibular lymph nodes, and gut associated lymphoid tissue. hypocellularity of the bone marrow **45 mg:** Mortality (see above) decreased activity, decreased appetite, abdominal distention, emesis, dehydration, decreased muscle tone, weakness, thinness, partly closed eye, salivation, red or black feces, soft/liquid feces, hunched posture, cold to touch, and moribundity Increased UREA, Creat Necropsy (early termination related): Dark gastrointestinal content Small thymus and spleen Microscopy: Gastrointestinal (only early terminated animals); necrosis of the mucosa and hemorrhage, erosion, and ulceration. lymphoid atrophy/necrosis in the thymus, spleen, mesenteric and mandibular lymph nodes, and gut associated lymphoid tissue. hypocellularity of the bone marrow

69506 GLP		0, 5, 10, 15 PO	6 month	**No NOAEL** HNSTD 10 mg/kg/day AP26113 C_{max} 485 ng/mL and $AUC_{(0-24)}$ 6175 h•ng/mL, on Day 181	Moribundity (15 mg/kg/day Males) as a results of hypoactivity, ataxia, hunched posture, thin body, pale/cool body and/or extremities, dermal atonia, and fecal observations. Early termination of dosing at Day 62. 1 M allowed a 56 day non-dosing recovery period. ≥**5 mg:** clinical pathology: decreased LYMP, WBC, RBCHC, HT lower spleen, testes, pituitary gland, and thymus weights Microscopy: kidney; retention of brown, finely granular pigment within the cytoplasm of tubular epithelial cells, most notable in the proximal convoluted tubules. Axillary lymph nodes: reduced lymphoid density, decreased number of lymphoid follicles. Reduced lymphocyte density in thymus. ≥**10 mg:** decreased retic (M) Decreased Cl (M), P Microscopy: reduced red pulp, irrgilar capsular surface (due to contraction of the spleen). Foamy alveolar macrophages in lung. **15 mg:** decreased retic (F) Decreasaed TP, Albumin, globulin (M), increased gluc, decreased Ca and microscopic findings in the kidneys, intestinal tract, lymphoid organs, and thymus, and low organ weights for spleen, testes, pituitary gland, and thymus

AP26113: brigatinib

Genotoxicity

The in vitro studies of genotoxicity showed that brigatinib is toxic to the cells and induced cell cycle arrest (9600382, 9600383, and 9800314). However, the in vivo chromosomal aberration test showed that brigatinib demonstrated potential for clastogenic effects caused by disruption of the mitotic apparatus through micronuclei formation in bone marrow polychromatic erythrocytes of male rats, when tested up to the MTD of 125 mg/kg/day.

Type of test / study ID / GLP	**Test system**	**Concentrations / Concentration range / Metabolising system**	**Results Positive / negative / equivocal**
Gene mutations in bacteria	Salmonella strains TA1535, TA1537, TA98, TA100 E. coli WP2uvrA	1.58 to 5000 µg/plate +/- S9	negative
Chromosome aberration in mammalian cells	Human peripheral blood lymphocytes	+/- S9	equivocal
Chromosomal aberrations in vivo	Mouse, micronuclei in bone marrow	10, 25, 50, 125 mg/kg/day p.o.	positive

Carcinogenicity

Carcinogenicity studies in animals were not conducted (see discussion on non-clinical aspects).

Reproduction Toxicity

Study type / Study ID / GLP	Species; Number Female / group	Route & dose	Dosing period	Major findings	NOAEL (mg/kg) & C_{max} & AUC
DRF Embryo-fœtal development 9000676 Non-GLP	6 F (TK: 6 F) Sprague Dawley	0, 5, 10, 15, 25 mg/kg/day PO	GD 6-17	**F0:** **25 mg:** lower BW gain, lower food cons GD 6-18 **F1:** **≥10 mg:** lower BW, increased resorptions **25 mg:** 1/6 total resorption Malformations in 3 litters (4 animals); subcutaneous edema over the cervical and/or thoracic region, cleft palate, and shortened lower jaw (mandibular micrognathia)	F0 F1
Embryo-fœtal development 9000674 GLP	20 F (TK: 6 F) Sprague Dawley	0, 5, 12.5, 25 mg/kg/day PO	GD 6-17	**F0:** **25 mg:** lower BW, lower BW gain, decreased food consumption GD 6-9 2/20 total resorptions **F1:** **≥12.5 mg:** decrease BW Skeletal variations; small incisors, incomplete ossifications of thoracic vertebrae and/or arches, pelvic bone, parietal, interparietal and/or frontal bones. Wavy, notched and/or absent ribs **25 mg:** Malformations in 13/20 litters: 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 gestroschisis (intestines protruding from herniated abdominal wall) Skeletal variations: fused ribs, displaced, absent or fused cervical and thoracic vertebrae, incomplete ossifications of sternebrae and xiphisternum	**F0** 12.5 mg/kg/day C_{max} 952 ng/mL $AUC_{(0-t)}$ 14400 h•ng/mL **F1** 5 mg/kg/day C_{max} 508 ng/mL $AUC_{(0-t)}$ 5290 h•ng/mL

Studies on fertility and early embryonic development or pre-and post-natal development were not performed.

Toxicokinetic data

Table 14: Overview of Toxicokinetics Studies with Brigatinib

Type of Study	Test System	Method of Administration	Doses (mg/kg)	GLP Compliance	Study or Report Number
14 day toxicity	Rat/Sprague-Dawley	Oral	0, 3, 10, 30, 100	No	ARP222
28 day toxicity	Rat/Sprague-Dawley	Oral	0, 15, 30, 60	Yes	805018
6 month toxicity	Rat/Sprague-Dawley	Oral	0, 7.5, 15, 25	Yes	69505
14 day toxicity	Monkey/Cynomolgus	Oral	0, 3, 10, 30	No	QAA00205
28 day toxicity	Monkey/Cynomolgus	Oral	0, 7.5, 15, 45	Yes	805020
6 month toxicity	Monkey/Cynomolgus	Oral	0, 5, 10, 15	Yes	69506
Embryofetal development	Rat/Sprague/Dawley	Oral	0, 5, 12.5, 25	Yes	9000674

Table 15: Terminal AUC(0-24) (h•ng/mL) at the End of the Dosing Phase in Rat and Monkey Toxicity Studies with Brigatinib

Daily Dose (mg/kg/day)	Duration of study	Rats		Monkeys	
		M	F	M	F
3	14 days		7180	1118[b]	
5	12 days		5290[a]		
5	6 months			3730	2820
7.5	6 months	18200	19000		
7.5	28 days			3408	3358
10	14 days		41120	3335[b]	
10	6 months			5900	6450
12.5	12 days		14400[a]		
15	28 days	21716	23550	8309	7584
15	6 months	37600	32700		8430
25	12 days		25500[a]		
30	14 days		131840	9079[b]	
30	28 days	40527	48890		
45	28 days; Day 1 data			24556	22604
60	28 days	38939	35762		
100	14 days		75086		

(a) in pregnant female rats
(b) combined genders; 1 monkey/sex

Table 16: Terminal Systemic Exposure (Combined Gender AUC(0-t)) at Reference Doses in Pivotal Nonclinical Toxicology Studies with Associated Exposure Multiples Relative to the GeoMean Steady State Human AUC(0 t) of 20276 h·ng/mL at the Maximum Clinical Dose of 180 mg/day Brigatinib

Study	Reference dose (mg/kg/day)	$AUC_{(0-t)}$ (h•ng/mL)	Exposure Multiple
28-day rat	15 (NOAEL)	22633	1.1
6-month rat	7.5 (STD10)	18600	0.9
28-day monkey	7.5 (NOAEL)	3383	0.2
Rat embryofetal	5 (NOAEL for embryofetal toxicity) 12.5 (NOAEL for maternal toxicity)	5290 14400	0.3 0.7
Rat micronucleus	125 mg/kg/day (MTD associated with minimal clastogenic response)	100000 (projected)	5
6-month monkey	10 (HNSTD)	6175	0.3

Local Tolerance

No local tolerance studies were performed. In the repeat dose toxicity studies, gastrointestinal toxicity was observed in animals that were terminated moribund. Furthermore, erosions atrophy and/or necrosis was observed in the gastrointestinal system in both nonclinical species used. Clinical signs consisting of emesis and/or loose stools were also observed in cynomolgus monkeys.

Other toxicity studies

Phototoxicity

A study was performed to ascertain the potential of brigatinib following a single PO dose of 15, 30 or 60 mg/kg/day to cause ocular or dermal toxicity in pigmented rats (20011745).

Table 17: Single-Dose Phototoxicity Study to Determine the Effects of Oral (Gavage) Administration of Brigatinib on Eyes and Skin in Pigmented Rats

20011745	**Report Title:** Single-Dose Phototoxicity Study[1] to Determine the Effects of Oral (Gavage) Administration of AP26113 on Eyes and Skin in Pigmented Rats					
Species/ Strain	**Method of Administration**	**Duration of Dosing**	**Dose (mg/kg)[a]**	**Gender and Number Per Group**	**Noteworthy Findings**	**Study No.**
				Female		
Rat/ CRL:LE (Long-Evans),	Oral	1 day[b]	0 (Vehicle) 15 30 60 50 (8-MOP)	5 5 5 5 3	No evidence of ocular or cutaneous phototoxicity. Comparator article 8-MOP: skin reactions in the lightly and darkly pigmented skin sites that demonstrated phototoxicity, validating the assay	20011745 (AP26113-11-1) (GLP)

(a) 25mM citrate buffer, pH 4.0; administered at a dose volume of 5 mL/kg

(b) Followed 4 hours later by UVR exposure [Instrumental UVR dose (mid-range ultraviolet, UVB) equivalent to 0.5 minimal erythema dose over a period of 30 ± 5 minutes.]

Impurities

No separate studies were performed to qualify impurities or metabolites. AP26123 was identified as an impurity in the drug substance, and a level of NMT 0.5% was proposed by the Applicant. AP26123 was also found to be a metabolite in both rat, cynomolgus monkey and human. In the nonclinical species used in the repeat dose studies (rat and cynomolgus monkey), AP26123 was detected in the toxicokinetic assessments, and AP26123 was identified as a metabolite of AP26113.

2.3.5. Ecotoxicity / environmental risk assessment

The applicant has provided an environmental assessment report, in which PBT screening as well as PBT assessment and PECsurfacewater is calculated. PECsurfacewater was refined by utilising prevalence data.

Table 18: Summary of main study results

Substance (INN / Invented Name): brigatinib					
CAS-number (if available): 1197953-54-0					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log P_{ow}	OECD107	1.62			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log P_{ow}	1.62			not B
	BCF	-			-
Persistence	DT50 or ready biodegradability	Not ready biodegradable			P
Toxicity	Acute 72 toxicity NOEC EC_{50} Chronic NOEC	 <0.009 mg/L 1.60 mg/L 3.02 mg/L			not T
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0036	µg/L			> 0.01 threshold (N)
Other concerns (e.g. chemical class)					(Y/N)
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Pseudokirchneriella subcapitata*	OECD 201	NOEC	41	µg/L	Endppoint growth
Daphnia magna. Reproduction Test	OECD 211	NOEC	915	µg/L	
Fish, Early Life Stage Toxicity Test/*Danio rerio*	OECD 210	NOEC	256	µg/L	Body length and body weight

Considering the above data, brigatinib is not expected to pose a risk to the environment.

Brigatinib is not readily biodegradable. However based on the results of the short and chronic toxicity assessment, the Daphnia reproduction and zebra fish early life cycle test it is unlikely that brigatinib drug product will pose a risk for the environment following its prescribed usage in patients.

2.3.6. Discussion on non-clinical aspects

Brigatinib is a novel, orally-active tyrosine kinase inhibitor (TKI). Primary targets are activated, mutant forms of anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1), which play important roles in non-small cell lung cancer (NSCLC) and other cancers.

In several in **vitro kinase assays as well as cell based assays** brigatinib was showed to inhibit ALK as well as 17 mutated variants of ALK, including G1202R. The G1202R mutation is associated with resistance to treatment with the currently approved ALK tyrosine kinase inhibitors. Brigatinib inhibits both native and mutated ALK at lower concentrations, and clinical Cmax following 180 mg/day is above the determined IC90 in all cases. However, the lower daily dose of 90 mg/day does not give the same result, where the IC90 of G1202R exceeds the projected Cmax.

In the in **vivo studies** brigatinib was shown to inhibit tumour growth as well as cause tumour regression at lower doses than crizotinib across several tumour models expressing e.g. EML4-ALK or NPM-ALK. At doses of up to 50 mg/kg/day of brigatinib, tumour regression and inhibition of ALK signalling was achieved, and the doses utilised was well tolerated. In **study ARP621**, intracranial tumours were generated in SCID mice, and the mice were subsequently treated with brigatinib (25 or 50 mg/kg/day). Mean survival time was increased in all treated groups, 62 days to more than 64 days (25 and 50 mg/kg/day respectively), compared to 28 days for the control group. The Applicant speculates that the efficacy of brigatinib in this mouse model of brain tumours would be due to enhanced CNS penetration, however, this was not shown in the tissue distribution studies, where CNS was highlighted as a tissue with very little brigatinib associated radioactivity. Although no evidence on CNS penetration was shown, it is supported that brigatinib administered orally, does show efficacy towards brain tumours in mice.

The safety pharmacology studies showed that following a single dose of brigatinib there were effects on the respiratory and cardiovascular systems, as well as the renal system. No effects were observed in the CNS study. Brigatinib did not show any potential for QT prolongation or neurofunctional effects, but identified potential for pulmonary effects (altered respiration rate; 1-2x the human C_{max} at the MHRD), cardiovascular effects (altered heart rate and blood pressure; at 0.5x the human C_{max} at the MHRD), and renal effects (reduced renal function; at 1-2.5x the human C_{max} at the MHRD) (SmPC, section 5.3). In the clinical setting, renal effects such as proteinuria, haematuria and renal impairment have been noted in lung cancer patients treated with brigatinib, and suggest a potential clinical correlate of the nonclinical renal safety pharmacology findings. Pulmonary (dyspnoea, hypoxia) and cardiovascular (bradycardia) effects have been in noted in cancer patients treated with brigatinib and suggest a potential correlation with the nonclinical cardiovascular and pulmonary safety pharmacology findings. In the toxicity studies, brigatinib had a multitude of effects, including moribundity and mortality at high doses. Toxicological effects were noted in multiple organs such as the gastrointestinal tract, eye, kidney, lung, liver, heart, pancreas, testes/epididymis, bone, hematopoietic system, and immune-system related organs. The principal dose-limiting nonclinical toxicities were gastrointestinal, cardiac, and renal effects. The systemic exposure associated with key toxicities in rat and monkey general toxicology studies and the rat embryofoetal study was generally at or below the human AUC.

Adverse reactions seen in animals at exposure levels similar to clinical exposure levels with possible relevance to clinical use were as follows: gastrointestinal system, bone marrow, eyes, testes, liver, kidney, bone, and heart. These effects were generally reversible during the non-dosing recovery period; however, effects in the eyes and testes were notable exceptions due to lack of recovery (see section 5.3 of the SmPC).

In repeated dose toxicity studies, lung changes (foamy alveolar macrophages) were noted in monkeys at ≥ 0.2 x the human AUC; however, these were minimal and similar to those reported as background findings in naive monkeys, and there was no clinical evidence of respiratory distress in these monkeys.

Carcinogenicity studies have not been performed with brigatinib which is acceptable, as brigatinib is intended for treatment for advanced cancer.

Brigatinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) or the mammalian cell chromosomal aberration assays, but slightly increased the number of micronuclei in a rat bone marrow micronucleus test. The mechanism of micronucleus induction was abnormal chromosome segregation (aneugenicity) and not a clastogenic effect on chromosomes. This effect was observed at approximately five fold the human exposure at the 180 mg once daily dose.

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

Brigatinib may impair male fertility. Testicular toxicity was observed in repeat-dose animal studies. In rats, findings included lower weight of testes, seminal vesicles and prostate gland, and testicular tubular degeneration; these effects were not reversible during the recovery period. In monkeys, findings included reduced size of testes along with microscopic evidence of hypospermatogenesis; these effects were reversible during the recovery period. Overall, these effects on the male reproductive organs in rats and monkeys occurred at exposures ≥ 0.2-times the AUC observed in patients at the 180 mg once daily dose. No apparent adverse effects on female reproductive organs were observed in general toxicology studies in rats and monkeys (see section 5.3 of the SmPC). The risk of embryofetal and developmental toxicity as a potential risk in the RMP and the effects on male and/or female fertility as missing information (see RMP).

Brigatinib showed no evidence of cutaneous or ocular phototoxicity after a single oral administered to pigmented Long-Evans rats.

The metabolite AP26123 and the impurities present in the brigatinib lots have been qualified in pivotal general toxicology studies.

On the basis of the submitted ERA, brigatinib is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The pharmacologic, pharmacokinetic and toxicological characteristics of brigatinib are well characterized.

2.4. Clinical aspects

2.5. Clinical aspects

2.5.1. Introduction

The pharmacokinetics of brigatinib have been evaluated in seven studies in healthy subjects and two studies in patients with malignant condition, mainly ALK+ NSCLC.

Two of the clinical studies in cancer patients are the basis for summarizing the clinical pharmacology of brigatinib: a first in human phase 1/2 study of brigatinib, AP26113-11-101, and a pivotal randomized

phase 2 study of brigatinib in patients with ALK+ NSCLC and prior progression on crizotinib, AP26113-13-201.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

GCP inspections at a CRO facility in USA and two investigator sites, located in Germany and Denmark were conducted between June-July 2017 in connection with the conduct of pivotal trial with protocol number AP26113-13-201.

Table 19: Clinical pharmacokinetic studies

Study Number and Description	Key Objective(s)	Treatment Regimen and Formulation	N
Study AP26113-13-102: Ethnobridging	To evaluate the safety, tolerability, and PK of brigatinib in Japanese and Caucasian healthy subjects	3 dose cohorts (90, 120, or 180 mg brigatinib) consisting of 8 Japanese (6 active; 2 placebo) and 8 Caucasian (6 active; 2 placebo) subjects each	48
Study AP26113-13-103: Preliminary Food Effect	To determine the effect of a high-fat meal on the PK of brigatinib compared to the fasted state in healthy subjects	180 mg of brigatinib single dose on Day 1 fasted and on Day 10 (or later) with food	10
Study AP26113-13-104: ^{14}C ADME	To understand the absorption, metabolism, and elimination pathways of brigatinib	single oral dose of 180 mg [^{14}C]brigatinib in solution	6
Study AP26113-15-105: DDI study with inhibitors and inducers of brigatinib metabolism	To evaluate the PK of brigatinib in the presence and absence of a strong CYP3A4 inhibitor (itraconazole) To evaluate the PK of brigatinib in the presence and absence of a strong CYP2C8 inhibitor (gemfibrozil) To evaluate the PK of brigatinib in the presence and absence of a strong CYP3A4 inducer (rifampin)	Three-Part, Open-Label, One Sequence Crossover Study: *Itraconazole:* 90 mg brigatinib alone on Day 1, itraconazole 200 mg BID on days 17 - 25, 90 mg brigatinib co-administered on Day 21. *Gemfibrozil*: 90 mg brigatinib alone on Day 1, gemfibrozil 600 mg BID on days 17 - 25, 90 mg brigatinib co-administered on Day 21. *Rifampin*: 180 mg brigatinib alone on Day 1, rifampin 600 mg QD on days 17 - 25, 180 mg brigatinib co-administered on Day 23.	60
Study AP26113-15-106: BE Study	To compare bioequivalence between 3 × 30 mg tablets and one 90 mg tablet	The study consisted of 2 dosing periods separated by a washout period of at least 16 days. In each dosing period, subjects received either three 30 mg brigatinib tablets or one 90 mg brigatinib tablet.	36
Study AP26113-16-109: Pivotal Food Effect	To formally assess the effect of a high-fat meal on the PK of a single oral dose of brigatinib, administered as the intended commercial 90 mg tablet formulation	Single doses of brigatinib (180 mg [two 90 mg tablets]) under fed (high-fat meal) versus fasting conditions.	21
Study AP26113-16-110: BE Study	To determine whether there is bioequivalence between 30 mg tablets and 180 mg tablets when given in equal doses	The study consisted of 2 dosing periods separated by a washout period of at least 16 days. In each dosing period, subjects received either 6 x 30 mg brigatinib tablets or one 180 mg brigatinib tablet.	36
Abbreviations: ADME = absorption, distribution, metabolism, and excretion; BE = bioequivalence; BID = twice daily; CYP = cytochrome P450; DDI = drug-drug interaction; PK = pharmacokinetics; QD = once daily			

Table 20: Clinical efficacy and safety studies

	Study AP26113-11-101	Study AP26113-13-201
Title	A Phase 1/2 Study of the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-Tumor Activity of the Oral ALK/EGFR Inhibitor AP26113	A Randomized Phase 2 Study of AP26113 in Patients with ALK-positive, Non-small Cell Lung Cancer (NSCLC) Previously Treated with Crizotinib
Study Design	Open label phase 1 dose escalation study with phase 2 expansion	Phase 2, randomized open label study of 2 dosing regimens of brigatinib
Primary Objectives	To determine the safety profile including maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs), determine the RP2D, examine the pharmacokinetics and describe preliminary anti-tumor activity of brigatinib	To determine the efficacy, as evidenced by objective response rate, and safety of brigatinib in patients with ALK+ locally advanced or metastatic NSCLC whose disease has progressed on therapy with crizotinib
Primary Efficacy Endpoints [a]	Phase 1: Determination of the recommended phase 2 dose (RP2D) Phase 2: Investigator-assessed ORR (RECIST v1.1)	Investigator-assessed Confirmed ORR (RECIST v1.1)
Patient Population	137 patients overall; 79 patients with locally advanced or metastatic ALK+ NSCLC (71 of which had prior treatment with crizotinib). The reminder of the patients had EGFR mutant and ROS1+ NSCLC, as well as other tumor types	222 patients with ALK+ locally advanced or metastatic NSCLC whose disease has progressed on therapy with crizotinib
Investigational Sites [b]	9 investigational sites (8 US, 1 EU)	71 investigational sites (15 US, 1 Canada, 38 Europe, 6 Australia, and 11 Asia)
Dosing	Phase 1: 3+3 dose escalation (30 mg daily to 300 mg daily) Phase 2: 3 dosing regimens were evaluated 90 mg QD 180 mg QD after a 7-day lead-in at 90 mg QD (90 mg QD → 180 mg QD) 180 mg QD	Arm A: 90 mg QD Arm B: 180 mg QD after a 7-day lead-in at 90 mg QD (90 mg QD → 180 mg QD)
Enrollment Period	First patient dosed: Sept 2011 Last patient first dose: July 2014	First patient dosed: June 2014 Last patient first dose: Sept 2015
Study Status	Ongoing; 42 patients overall (36 ALK+ NSCLC patients) still on study treatment at time of data extraction	Ongoing; 140 patients still on study treatment at time of data extraction
Data Extraction Date for Initial Submission	31 May 2016	31 May 2016

Abbreviations: ALK = anaplastic lymphoma kinase; DLT = dose limiting toxicity; EGFR = epidermal growth factor receptor; EU = European Union; MTD = maximum tolerated dose; NDA = new drug application; NSCLC = non-small cell lung cancer; QD = once daily; ORR = objective response rate (RECIST v1.1); RECIST = Response Evaluation Criteria in Solid Tumors (version 1.1); RP2D = recommended phase 2 dose; QD = once daily; US = United States; 90 mg QD → 180 mg QD = 180 mg QD with a 7-day lead-in at 90 mg QD

[a] See Section 1.5.1.5, Module 2.7.3 Summary of Clinical Efficacy for secondary efficacy endpoints for both studies

[b] Sites with enrolled patients

Additionally, population PK analysis was conducted to evaluate the effect of subject characteristics.

2.5.2. Pharmacokinetics

Single dose and steady state PK was investigated in the clinical study AP26113-11-101 in patients. Clinical studies to investigate food effect, drug-drug interactions, ethnobridging Caucasian/Japanese, bioequivalence and mass balance (ADME) was conducted in healthy subjects.

The two LC-MS-MS based bioanalytical methods for brigatinib and the metabolite, AP26123, in human plasma are adequately validated. Assay performance, in terms of inter-assay precision and inter-assay relative error is considered acceptable.

The brigatinib PK was best described by a three-compartment model with delayed, first-order absorption. A flexible transit compartment absorption model (TCAM) was included to describe variable absorption between subjects.

Absorption

Brigatinib is an oral administered ALK inhibitor. The recommended dose is 90 mg once daily for one week followed by 180 mg once daily.

In Study 101, following administration of a single oral dose of brigatinib (30-240 mg) in patients, the median time to peak concentration (Tmax) was 1-4 hours postdose. After a single dose and at steady state, systemic exposure was dose proportional over the dose range of 60-240 mg once daily. Modest accumulation was observed upon repeated dosing (geometric mean accumulation ratio: 1.9 to 2.4). The geometric mean steady state Cmax of brigatinib at doses of 90 mg and 180 mg once daily was 552 and 1452 ng/mL, respectively, and the corresponding AUC_{0-T} was 8165 and 20276 h·ng/mL, respectively (see section 5.2 of the SmPC).

- **Bioavailability**

The absolute oral bioavailability of brigatinib in humans has not been determined.

- **Influence of food**

In two separate studies, brigatinib absorption under fasting and fed conditions was evaluated. In both the exploratory (AP26113-13-103), as well as the pivotal food-effect studies (AP26113-16-109), plasma brigatinib Cmax was reduced by 24%(AP26113-13-103), to 13%(AP26113-16-109) and Tmax was delayed by 3.0 to 3.5 hours with a high fat meal. However, in both food effect evaluations, changes in the initial rate of absorption did not result in changes in the overall exposure of brigatinib (either AUC0-t or AUC0-inf). In the pivotal clinical studies, patients were instructed to self-administer brigatinib orally without regards to meals.

Table 21: ANOVA Results for Brigatinib Test to Reference Outcomes (PK Set) (AP26113-13-103)

Parameter	Brigatinib Comparison	LS Mean Difference (SE)	Estimated Geometric Mean Ratio (%)	90% CI (Lower, Upper)
C_{max} (N=8)	fed versus fasted	-0.273 (0.0803)	76.074	67.766, 85.401
AUC_{0-t} (N=8)	fed versus fasted	-0.029 (0.680)	97.150	88.086, 107.147
$AUC_{0-\infty}$ (N=7)	fed versus fasted	0.000 (0.0837)	100.023	88.163, 113.479

Source: CSR AP26113-13-103 Tables 14.2.3, 14.2.5, and 14.2.6.
AUC_{0-t}=area under the plasma concentration-time curve from time 0 to time of last measured concentration; $AUC_{0-\infty}$=area under the plasma concentration-time curve from time 0 to infinite time, CI=confidence interval, C_{max}=maximum concentration, LS=least squares, PK=pharmacokinetic, SE=standard error.
Note: Subjects 9003 and 9010 were excluded from this analysis as they did not receive both treatments. Unreliable $AUC_{0-\infty}$ values for Subjects 9015 and 9016 were excluded from the statistical analysis.

Table 22: Comparison of Brigatinib Cmax, AUC0-t, and AUC0-∞ (AP26113-16-109)

Parameter	Comparison	LS Mean Difference (SE)	GeoMean Ratio* (%)	90% CI (Lower, Upper)
C_{max} (N=21)	brigatinib fed vs brigatinib fasted	–0.139 (0.0613)	87.016	78.261, 96.752
AUC_{0-t} (N=21)	brigatinib fed vs brigatinib fasted	–0.020 (0.0531)	97.985	89.396, 107.399
$AUC_{0-\infty}$ (N=21)	brigatinib fed vs brigatinib fasted	–0.020 (0.0529)	97.998	89.430, 107.386

Source: AP26113-16-109 CSR Table 14.2.3

Table 23: Comparison of Brigatinib Tmax (AP26113-16-109)

Contrast (Difference)	Statistic	Result	P-value
Brigatinib fed vs brigatinib fasted	Median	2.0	0.0004
	Range	-3.50, 4.00	

Source: AP26113-16-109 CSR Table 14.2.4

- **Bioequivalence**

Two clinical studies (Study AP26113-15-106 and Study AP26113-16-110) have been conducted to establish the bioequivalence of brigatinib 90 and 180 mg oral tablets to 30 mg oral tablets in healthy volunteers.

Bioequivalence Study 90 mg versus 30 mg Tablet (Study AP26113-15-106): Median brigatinib Tmax was 2.0 hours postdose for three 30 mg tablets (range 1 to 4 hours) and 2.5 hours postdose for one 90 mg tablet (range 1 to 6 hours). The observed GeoMean Cmax was similar for the 2 treatments, with values of 354.8 ng/mL for three 30 mg brigatinib tablets and 352.7 ng/mL for one 90 mg brigatinib tablet. GeoMean values for AUC0-t and AUC0-∞ were also similar following administration of three 30 mg brigatinib tablets (6680 h·ng/mL and 6737 h·ng/mL, respectively) and one 90 mg tablet (6924 h•ng/mL and 7133 h•ng/mL, respectively).

Table 24: Comparison of Brigatinib Cmax, AUC0-t, and AUC0-∞- Bioequivalence population (AP26113-15-106)

Parameter	LS Mean Difference (SE)	GeoMean Ratio (%)	90% Confidence Interval (Lower, Upper)
C_{max} (ng/mL)	0.016 (0.0405)	101.616	94.878, 108.833
AUC_{0-t} (h·ng/mL)	0.022 (0.0269)	102.232	97.677, 107.000
$AUC_{0-\infty}$ (h·ng/mL)	0.022 (0.0269)	102.248	97.692, 107.017

Source: AP26113-15-106 CSR Table 14.2.3

Bioequivalence Study 180 mg versus 30 mg Tablet (Study AP26113-16-110): Median brigatinib Tmax was similar between the two treatments - 2.0 hours postdose for six 30 mg tablets (range 1 to 6 hours) and 2.0 hours postdose for one 180 mg tablet (range 1 to 4 hours). The observed GeoMean Cmax was similar for the 2 treatments, with values of 756.5 ng/mL for six 30 mg brigatinib tablets and 766.3 ng/mL for one 180 mg brigatinib tablet.

Geometric mean values for AUC0-t and AUC0-∞ were also similar following administration of six 30 mg brigatinib tablets (13614 h·ng/mL and 13881 h·ng/mL, respectively) and one 180 mg tablet (13229 h•ng/mL and 13466 h•ng/mL, respectively). Variation in Cmax and AUC0-t was moderate for both treatments, with geometric CVs of 36.9% and 37.6%, respectively, for the six 30 mg tablets and 36.1% and 36.7%, respectively, for the one 180 mg tablet. The mean and median brigatinib t½ values for both treatments were similar.

Table 25: Comparison of Brigatinib Cmax, AUC0-t, and AUC0-∞ Bioequivalence Population (AP26113-16-110)

Parameter	LS Mean Difference (SE)	GeoMean Ratio (%)	90% Confidence Interval (Lower, Upper)
C_{max} (ng/mL)	0.035 (0.0372)	103.586	(97.249, 110.336)
AUC_{0-t} (h·ng/mL)	0.016 (0.0294)	101.602	(96.644, 106.814)
$AUC_{0-\infty}$ (h·ng/mL)	0.014 (0.0291)	101.441	(96.540, 106.592)

Source: AP26113-16-110 CSR Table 8

Comparison was 1 × 180 mg tablet (test) vs 6 × 30 mg tablets (reference). Estimates and CI limits of the LSM differences for the natural log values were exponentiated and multiplied by 100.

Distribution

In patients given brigatinib 180 mg QD, (study AP26113-11-101) the GeoMean (coefficient of variation; CV%) apparent volume of distribution unadjusted for bioavailability (V_z/F) of brigatinib at steady state was 153.4 L (46.6%). Brigatinib has high in vivo binding to plasma proteins (91 %) and low affinity to human red blood cells (0.69 blood/plasma partition ratio).

Results from in vitro transporter studies suggest that brigatinib is a substrate of P-gp and BCRP, but not a substrate of OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, MATE2K, or BSEP.

Elimination

In vitro studies indicate that CYP2C8 and CYP3A4 are the major isozymes responsible for brigatinib metabolism, with minor contribution from CYP3A5.Metabolic clearance is mainly N-demethylation (forming the active metabolite M36) and cysteine conjugation. The contribution of the cysteine conjugation pathway is minor compared to demethylation. No multi-modality in the observed clearance distribution was identified and impact of genetic polymorphisms in CYP2C8 and CYP3A on PK is not expected. AP26123 is an active metabolite with comparable PK, though a slightly longer T½ and similar or slightly reduced potency against ALK and EGFR. The metabolite accounted for < 3.5 % of the circulation radioactivity in the ADME study.

An ADME/mass balance study was conducted with [14C]-Brigatinib in healthy volunteers (Study AP26113-13-104). Of the 180 mg [^{14}C]brigatinib oral dose administered, 47.87%, 26.88%, and 9.09% of the radioactive dose was excreted as unchanged brigatinib, M36 (N-desmethyl brigatinib; AP26123), and M28 (brigatinib cysteine conjugate), respectively in urine and feces combined. The estimated CLss/F of brigatinib at the recommended 180 mg dose is 12.71 L/h (CV=67.5%, N=63). The median terminal elimination half-life of brigatinib at steady state at a dose of 180 mg QD was 23.9 hours, resulting in a 2-fold accumulation at steady state. Following oral administration of [14C]brigatinib, parent brigatinib was the major circulating radioactive component accounting for 91.5% of the plasma radioactivity. AP26123 was the principal metabolite observed and was present at 3.5% in the plasma. In patients, at steady state, the plasma AUC of AP26123 was < 10% of brigatinib exposure.

The total recovery of a 180 mg [^{14}C]brigatinib dose was 89.75±1.44%, of which 24.99±1.89% and 64.76±2.36% were recovered in urine and feces, respectively. Unchanged brigatinib represented 41% and 86% of the total radioactivity in faeces and urine, respectively, the remainder being metabolites.

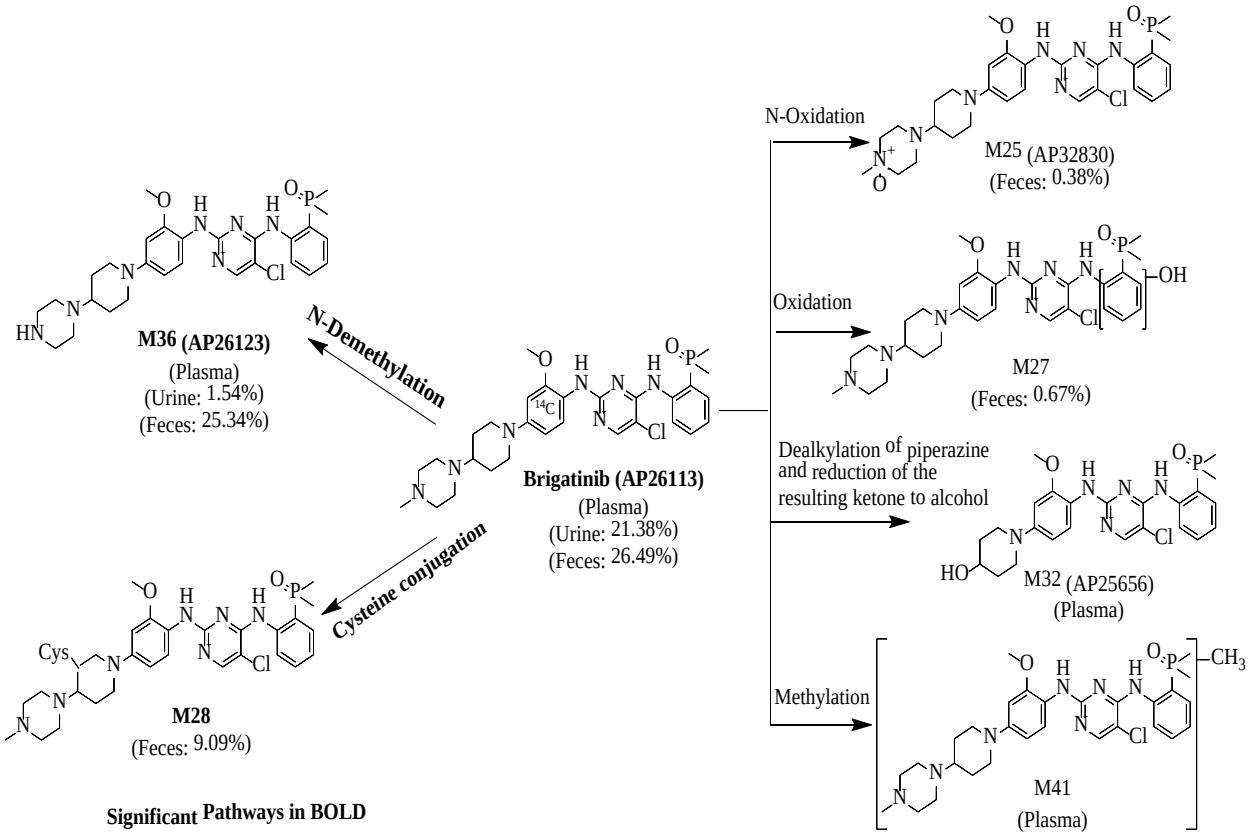


Figure 11: Proposed *In Vivo* Metabolic Pathways of Brigatinib Following Single Dose Oral Administration of 180 mg [^{14}C]Brigatinib to Healthy Male Subjects

Dose proportionality and time dependencies

- **Dose proportionality**

Dose proportionality was assessed in study AP26113-11-101. After single (C1D1) and repeated (C2D1) doses, systemic exposure increased in a dose-dependent manner in the dose range of 30–240 mg QD. A dose proportional increase in brigatinib Cmax and $AUC_{0-\tau}$ was observed over the dose range of 60-240 mg QD. At the 90 mg and 180 mg QD doses, the GeoMean steady state Cmax was 552.02 and 1451.7 ng/mL, respectively, and the corresponding $AUC_{0-\tau}$ was 8164.6 and 20276 h·ng/mL, respectively. At the brigatinib oral dose of 180 mg QD, for the evaluable 63 patients, GeoMean estimates (CV%) of CLss/F, apparent volume of distribution (Vz/F) and half-life were 12.7 L/h (67.5%), 153.4 L (46.6%) and 23.9 h (29.9%), respectively. These characteristics lead to modest drug accumulation (mean accumulation ratio [SD] in 180 mg cohort was 2.1 [0.4] at steady state).

- **Time dependency**

In study AP26113-11-101, at the brigatinib oral dose of 180 mg QD, for the evaluable 63 patients, GeoMean estimates (CV%) of CL_{ss}/F, apparent volume of distribution (V_z/F) and half-life were 12.7 L/h (67.5%), 153.4 L (46.6%) and 23.9 h (29.9%), respectively. Mean accumulation ratio [SD] in 180 mg cohort was 2.1 [0.4] at steady state.

In Study AP26113-13-201, GeoMean steady state predose (trough) brigatinib concentrations at steady state in Cycles 2, 3, 4, and 5 were similar, and ranged from 168.2 to 225.5 nanogram (ng)/mL for 90 mg QD (Arm A), and 398.0 to 466.9 ng/mL for 90 mg QD → 180 mg QD. This was in close

agreement with GeoMean concentrations of 226.3 and 519.9 ng/mL at 24 hours following the Cycle 2 Day 1 dosing at 90 mg and 180 mg QD, respectively, in Study AP26113-11-101.

Special populations

Population PK analyses of pooled data from 5 clinical studies with brigatinib (AP26113-11-101, AP26113-13-201, AP26113-13-102, AP26113-13-103, and AP26113-15-105) evaluated the effect of body weight, sex, age, race, liver enzyme levels, and creatinine clearance (CLCR) on brigatinib PK.

- **Race**

Ethnobridging Study (Study AP26113-13-102) was a double blind, randomized, placebo controlled, single ascending dose study of orally administered brigatinib in healthy subjects (24 Japanese and 24 Caucasian subjects). Single doses of brigatinib tested were 90 mg, 120 mg and 180 mg administered under fasting conditions. The arithmetic mean Cmax increased with increase in dose for Japanese and Caucasian subjects over the dose range of 90 mg to180 mg. There was also higher variability for both Cmax and AUC0-∞ with Caucasians compared with Japanese. The mean AUC0-∞ increased from 6064 h•ng/mL and 6782 h•ng/mL for Japanese and Caucasian subjects at 90 mg, respectively, to 9910 h•ng/mL and 12149 h•ng/mL for Japanese and Caucasian subjects at 180 mg, respectively.

- **Elderly**

No studies have been performed to evaluate brigatinib pharmacokinetics in elderly patient populations. As part of the integrated population pharmacokinetic analysis completed for brigatinib the effect of baseline patient age (years) was considered. The median (range) age of the PopPK study population (n=443) was 52 (19 to 83) years. Brigatinib CL/F was identified to decrease with increasing age by 0.7% per year. A subject of 75 years old is expected to have a 29.2% lower CL/F compared to a 20 year old subject which corresponds to a 41.2% higher AUC0-24.

Table 26: Number of Patients in Each Specified Age Category

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
PK Trials	70/443	16/443	0/443

- **Impaired renal function**

Clinical study AP26113-15-108, is an open-label, single-dose, parallel-group, in-patient, non-randomized study, investigating the effect of chronic renal impairment on brigatinib clearance.

Unbound AUC_{0-INF} was 94% higher in patients with severe renal impairment (eGFR < 30 mL/min, N=6) as compared to patients with normal renal function (eGFR ≥ 90 mL/min, N=8).

PK in patients with mild or moderate renal impairment has not been investigated, though this was originally planned.

The pharmacokinetics of brigatinib is similar in patients with normal renal function and in patients with mild or moderate renal impairment (eGFR ≥ 30 mL/min) based on the results of population pharmacokinetic analyses.

Creatinine clearance was not found to be a relevant covariate in the Pop PK analysis.

- **Impaired hepatic function**

Clinical study AP26113-15-107 was an open-label, single-dose, parallel-group, in-patient, non-randomized study conducted in subjects with varying grades of chronic hepatic impairment (6 patients with Child-Pugh A, B, C, respectively) and 9 matched healthy volunteers. Unbound PK parameters were unaffected by mild and moderate hepatic impairment (Child-Pugh A and B), but patients with severe hepatic impairment (Child-Pugh C) had increased exposure, including a 37 % increase in $AUC_{0\text{-}inf}$ compared to healthy subjects with normal hepatic function. Hepatic CYP3A is the major CYP isozymes (51 %) responsible for brigatinib metabolism, and CYP2C8 a minor metabolic pathway (15 %).

The population PK analysis dataset included 369 subjects with normal hepatic function, 68 subjects with mild hepatic impairment, 5 subjects with moderate hepatic impairment, and 1 subject with severe hepatic impairment. Brigatinib CL/F and dose-normalized AUC estimates were similar between subjects with normal hepatic impairment and subjects with mild hepatic impairment.

- **Age, body weight and albumin**

No paediatric studies have been conducted.

Relevant covariates with potential to influence distribution and/or elimination of brigatinib were investigated. Age, body weight and albumin were found in the Pop PK analysis to have impact on the PK of brigatinib.

Weight as covariate had impact on PK in the PopPK analysis with increase in clearance (CL/F increase with 1.0% for every kg increase in body weight) and therefore decrease in exposure. Age was a significant covariate in the PopPK analysis with a CL/F decrease of 0.6 % per year. Brigatinib CL/F was identified to increase with increasing albumin concentrations. Across a normal range of albumin concentrations of 34 to 54 g/L, CL/F is expected to change 30.4% (from 11 L/h to 14.4 L/h).

Body weight quartiles had considerable overlap for $AUC_{t,ss}$, $C_{max,ss}$ and $C_{min,ss}$. Though a clear trend of reduction in exposure with increasing body weight was observed, this had no clinical impact on safety and efficacy.

- **Intra-/inter-individual variability**

In the clinical study AP26113-11-101, PK parameters were estimated for brigatinib in patients receiving escalating oral doses (range 30-240mg) on Day 1 of cycles 1 and 2. Moderate to high degree of inter-individual variability was observed in the Cmax and AUC for both C1D1 and C2D1 (CV% ranging from 11% to 119 %). Inter-occasion variability % for Cmax and $AUC_{0\text{-}t/24}$ in healthy subjects and patients was < 17 % and ≤ 47% respectively. The median time to peak concentration (Tmax) was 1 to 4 hours postdose.

Pharmacokinetic interaction studies

In vitro studies do not indicate that either brigatinib or the metabolite AP26123 have the potential to inhibit other CYP-enzymes and cause drug-drug interactions in vivo if co-administered with medications primarily metabolized by CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6.

Brigatinib is a substrate of the transporters P-gp and BCRP and has in vitro inhibitory effect on both P-gp, BCRP, OCT1, MATE1 and MATE2K at clinically relevant concentrations. No further in vivo studies have been conducted to investigate these transporters.

As part of the PBPK analysis, 2 separate models were developed. One model (Model A) assumed that the unchanged brigatinib in faeces was due to unabsorbed drug, and therefore assigned a fraction absorbed (fa) of 0.63 on the basis of the mass balance data from Study AP26113-13-104. The second model (Model B) used a fa value of 1, based on the assumption of complete absorption of brigatinib and attribution of biliary clearance to explain the unchanged drug in faeces. Importantly, both PBPK models were able to generate plasma concentration-time profiles and exposures of brigatinib that were consistent with observed data. Additionally, both models were able to capture the observed effects of itraconazole and rifampicin on the pharmacokinetics of brigatinib. The PBPK model-predicted geometric mean Cmax and AUC ratios for brigatinib with and without itraconazole coadministration were within 1.10-fold and 1.04-fold of the observed values for Model A and Model B, respectively. Similarly, the PBPK model-predicted geometric mean Cmax and AUC ratios for brigatinib with and without rifampicin coadministration were within 1.20-fold and 1.28-fold of the observed values for Model A and Model B, respectively. The comparable results between the two PBPK models indicate that the disposition of brigatinib can be explained irrespective of the underlying mechanism (ie, incomplete absorption, biliary clearance) responsible for the presence of unchanged brigatinib in the faeces.Because Model B included a biliary clearance component for brigatinib, it was used to assess the worst-case scenario for P-gp inhibition by assuming that a virtual P-gp inhibitor completely abrogated biliary clearance. The predicted geometric mean Cmax and AUC ratios for brigatinib in the presence versus absence of such a virtual P-gp inhibitor were 1.07 and 1.41, respectively. This worst case 41% increase in brigatinib systemic exposure (AUC) is not thought to be clinically meaningful when considered in the context of the observed variability in AUC (62% coefficient of variation in the area under the plasma concentration-time curve during a dosing interval [AUC0-tau] after repeat dose administration of 180 mg in Study AP26113-11-101).

The DDI study AP26113-15-105 was conducted to determine if strong inhibitors of CYP2C8 or CYP3A4 (gemfibrozil and itraconazole, respectively) and a strong inducer of both enzymes, as well as P-gp, (rifampin) alter the single dose PK of brigatinib in healthy subjects. The DDI study was a single-center, 3-part, open-label, single-dose, 1-sequence, crossover study of the effects of gemfibrozil (Part 1), rifampin (Part 2), and itraconazole (Part 3) when each inhibitor or inducer was coadministered with brigatinib in healthy subjects.

- **Itraconazole**: Co-administration with brigatinib caused an increase in Cmax of 21.2 %,a 2-fold increase in AUC0-inf and an increase of AUC_{0-120} by 82% (< 2-fold), relative to a 90 mg brigatinib dose administered alone.

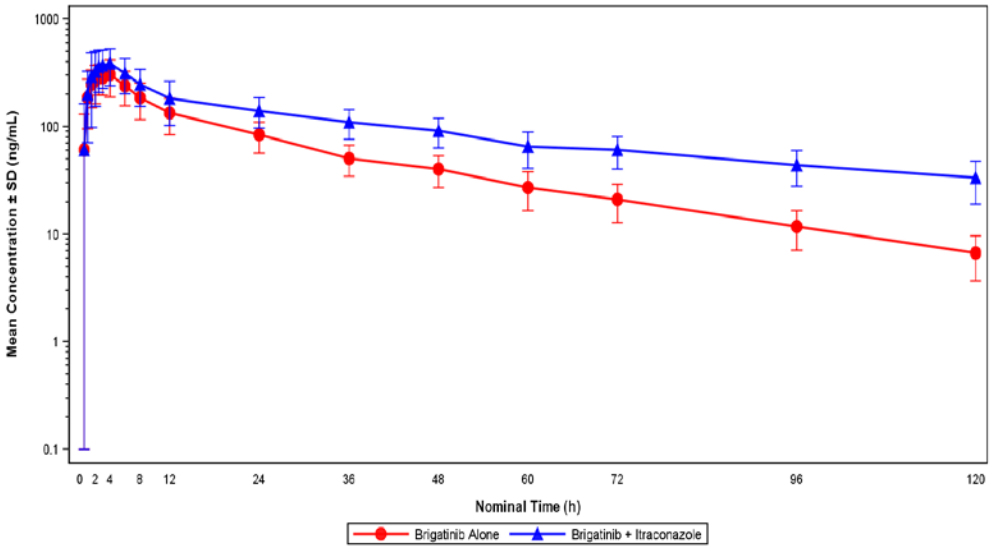


Figure 12: Part 3 (Effects of Itraconazole): Mean (±SD) Brigatinib Plasma Concentration VersusTime Profiles – PK Population (Study AP26113-15-105)

- **Gemfibozil** is a strong CYP2C8 inhibitor in vitro. In healthy subjects, coadministration of multiple 600 mg twice daily doses of gemfibrozil, a strong CYP2C8 inhibitor, with a single 90 mg brigatinib dose reduced brigatinib C_{max} by 41%, $AUC_{0\text{-}INF}$ by 12%, and $AUC_{0\text{-}120}$ by 15%, relative to a 90 mg brigatinib dose administered alone (SmPC, section 4.5).

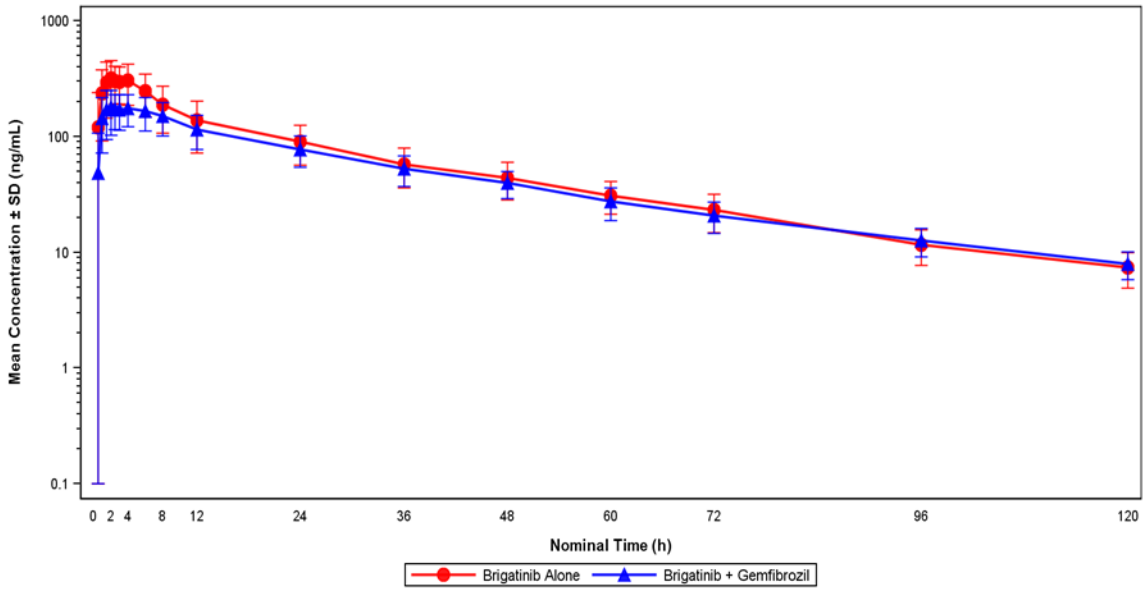


Figure 13: Part 1 (Effects of Gemfibrozil): Mean (±SD) Brigatinib Plasma Concentration Versus Time Profiles – PK Population (Study AP26113-15-105)

PBPK modelling approach to further characterise gemfibrozil DDI and showed that the geometric mean Cmax and AUC0-INF ratios for brigatinib with versus without gemfibrozil co-administration were 1.03 (trial range: 1.02-1.04) and 1.15.

- In healthy subjects, coadministration of multiple 600 mg daily doses of rifampicin, a strong CYP3A inducer, with a single 180 mg brigatinib dose decreased brigatinib C_{max} by 60%, $AUC_{0\text{-}INF}$ by 80% (5-fold), and $AUC_{0\text{-}120}$ by 80% (5-fold), relative to a 180 mg brigatinib dose administered alone (SmPC section 4.5).

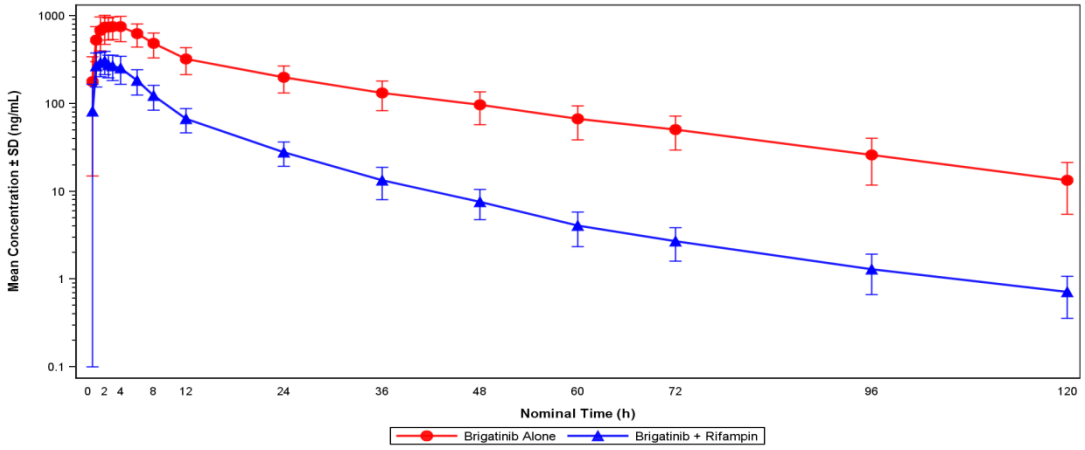


Figure 14: Part 2 (Effects of Rifampin): Mean (±SD) Brigatinib Plasma Concentration VersusTime Profiles – PK Population (Study AP26113-15-105)

The potential for reversible DDIs via inhibition of CYP3A4/5 by brigatinib has been investigated using PBPK modelling. The predicted geometric mean Cmax and AUC ratios for midazolam with and without co-administered brigatinib were both 1.07, which indicates that brigatinib is unlikely to produce clinically significance inhibition of CYP3A in vivo.

Model-predicted changes in brigatinib systemic exposures during coadministration with moderate CYP3A inhibitors (e.g., verapamil and diltiazem) or inducers (e.g., efavirenz) were also investigated using PBPK modelling and were found to be similar irrespective of the estimated unbound fraction value. AUC of brigatinib was increased by approximately 40 % when coadministered with verapamil or diltiazem according to the PBPK model. No uniform dose reduction is required, but patients should be closely monitored. The PBPK model predicted a significant decrease in brigatinib AUC if coadministered with efavirenz. Coadministration of brigatinib with moderate CYP3A inducers should be avoided.

Table 27: Comparison of Model-Predicted Geometric Mean C_{max} and AUC_{0-INF} Ratios for Brigatinib in the Presence versus Absence of Moderate CYP3A Inhibitors or Inducers Using an Unbound Fraction of 0.343 or 0.088

	Unbound Fraction of 0.343		Unbound Fraction of 0.088	
CYP3A Inhibitor/Inducer	C_{max} Ratio	AUC_{0-INF} Ratio	C_{max} Ratio	AUC_{0-INF} Ratio
Verapamil	1.08	1.32	1.15	1.38
Diltiazem	1.08	1.40	1.13	1.43
Efavirenz	0.85	0.52	0.83	0.53

Source: PBPK Report Addendum, Table 1.
AUC_{0-INF} = area under the plasma concentration-time curve from time zero to infinity, C_{max} = maximum observed plasma concentration.

2.5.3. Pharmacodynamics

No dedicated clinical pharmacodynamics studies have been conducted with brigatinib.

Mechanism of action

Brigatinib was designed to be a potent, selective inihibitor of ALK capable of overcoming mechanisms associated with resistant to other ALK inhibitors including crizotinib, ceritinib and alectinib, including point mutations in the ALK kinase domain (KD).

Brigatinib is a substantially more potent inhibitor of ALK than crizotinib. Across a panel of 8 ALK+ cell lines, brigatinib inhibited ALK (median 50% inhibitory concentration of 10 nanomolar [nM]) with 12-fold greater potency than crizotinib. In in vivo models, compared to brigatinib, higher dose and plasma

levels of crizotinib were required to achieve a similar degree of efficacy and ALK inhibition (see non-clinical aspects).

Primary and Secondary pharmacology

Primary pharmacology

Brigatinib is a potent and selective inhibitor of ALK in in vitro kinase assays. The activity of EML4-ALK and 17 mutated forms were inhibited in vitro by ≤ 500 nM brigatinib, i.e. therapeutic concentrations.

The steady state GeoMean Cmax (2485 nM), free Cmax (852 nM), and Cmax values corrected for the functional effects of protein binding (1243 nM) in patients dosed with brigatinib at 180 mg QD, exceeded the IC90 values for native ALK (38 nM) and all 17 ALK resistance mutants tested (range 22-762 nM), including L1196M and G1202R (study AP26113-11-101). Brigatinib has a 12-fold higher potency than crizotinib in vitro.

Secondary pharmacology

No thorough QT study has been conducted. Brigatinib has a low potential to cause QT prolongation based on in vitro hERG data, and non-clinical studies in cynomolgus monkeys did not find significant ECG changes following 28 days administration.

Changes from baseline in QTc interval were investigated in the clinical study AP26113-11-101. The mean change from baseline for QTcF ranged from -5.1 ms to +8.8 ms over the dose groups without any relationship to dosage. Among all patients treated with brigatinib the mean time averaged change from baseline for QTcF was -0.1 ms. No patient had an increase in QTcF > 60 ms or a new QTcF > 500 ms. Based on an independent review of the ECGs identified by the centralized core lab as having new morphologic ECG findings, no patients developed new abnormal U waves. Approximately 15% of subjects met the non-specific criterion of a 30-60 ms change from baseline among the various dose groups without any correlation with brigatinib dosage. There was no exposure-response relationship between brigatinib concentration and QTcF identified the study.

Exposure-response relationship

Exposure-response analysis has been conducted with data from two clinical studies.

In study AP26113-13-201 brigatinib exposure parameter was C_{trough} at steady state. There was overall no significant association between brigatinib exposure (in quartiles) and objective response. Response was high across all exposure cohorts and quartiles of exposure. Patients with confirmed intracranial objective response had higher exposure. A trend of increased probability of SAEs, EOPE and discontinuations was seen with higher C_{max} and higher GeoMean trough showed a trend in more SAEs and Grade 3 events. A clear trend of higher exposure in lower weight patients is seen, but without a clinical relevant impact on safety or efficacy.

Data from the two studies AP26113-11-101 and AP26113-13-201 support the recommended dose with 90 mg once daily for a week followed by 180 mg once daily. High and durable response rates are observed with the recommended dose with no increasing trend with higher exposure and an up going trend for AEs with higher exposure supports not to dose higher than 180 mg once daily.

Dosing recommendations for brigatinib are based on a combination of factors: primarily based on clinical efficacy and safety findings, supported by PK and exposure response analyses as well as nonclinical studies.

In the pivotal study, Study AP26113-13-201, comparing 90 mg QD to 90 mg QD → 180 mg QD, the following is observed:

1. A numerical increase in investigator-assessed confirmed ORR (53.6% [97.5% CI: 42.6, 64.5] for 90 mg QD → 180 mg QD and 44.6% [97.5% CI: 34.0, 55.6] for 90 mg QD), supported by IRC assessments (52.7% [95% CI: 43.0, 62.3] for 90 mg QD → 180 mg QD and 48.2% [95% CI: 38.7, 57.9] for 90 mg QD).

2. A clinically meaningful difference in PFS median values (12.9 vs 9.2 months) favoring 90 mg QD →180 mg QD vs 90 mg QD and a post-hoc analysis to aid in dose selection that showed HR for PFS between doses of 0.55 (95% CI: 0.35, 0.86). In addition, the IRC-assessment of PFS (15.6 vs. 9.2 months, respectively; post-hoc HR of 0.57 [95% CI: 0.36, 0.89]) supported the investigator-assessed PFS findings.

3. Greater intracranial, IRC-assessed confirmed ORR for 90 mg QD →180 mg QD vs. 90 mg QD, particularly in patients with measurable, active metastases (at baseline) (73.3% [11/15]

and 42.1% [8/19]), but also in patients with measurable metastases (66.7% [12/18] vs. 42.3% [11/26])

4. Higher 1 year probability of survival (OS) for 90 mg QD →180 mg QD (79.5%) vs. 90 mg QD (70.6%)

5. Fewer discontinuations due to documented progressive disease in 90 mg QD →180 mg QD (14.5% [16/110]) vs. 90 mg QD (25.9% [29/112]).

6. Fewer deaths within 30 days of last dose of study drug for 90 mg QD → 180 mg QD ([14.6% [18/123] in 90 mg mg QD vs. 6.5% [9/138] in 90 mg QD →180 QD] and specifically due to neoplasm progression (8.1% [10/123] in 90 mg QD vs. 3.6% [5/138] in 90 mg QD →180 mg QD]

The safety findings in Study AP26113-13-201 suggest that brigatinib has an acceptable safety profile for both regimens evaluated. Deaths due to disease is the largest risk in this patient population. The most common cause of death during treatment or within 30 days of last dose was neoplasm progression and there were fewer such deaths in this timeframe in Arm B (Arm A vs Arm B: 8.3% vs 3.6%); deaths due to non-disease progression AEs are actually higher in Arm A, suggesting this difference is not a treatment related effect.

The PK data from Study AP26113-11-101 showed that the average steady state brigatinib plasma concentrations in patients dosed at 90 mg QD or 180 mg QD were found to exceed the IC50 values for native EML4 ALK and all 17 resistance mutants by at least 2-fold, with the exception of the G1202R mutant.

Overall, for Study AP26113-11-101 in patients with advanced malignancies, the combination of high response rates and long PFS in the lower quartiles of exposure, along with fewer early discontinuations, a lower risk of early onset pulmonary adverse events, and a lower risk of SAEs supported the doses chosen for further evaluation study: 90 mg QD and 180 mg QD with 7-day lead-in at 90 mg QD.

2.5.4. Discussion on clinical pharmacology

The clinical pharmacology of brigatinib has been thoroughly investigated in both healthy subjects and patients and has been described using non-compartmental analysis and population PK model. The pharmacokinetics of brigatinib and relevant covariates have been adequately described, including PK studies in patients with renal and hepatic impairment. Population PK analysis was conducted to evaluate the effect of subject characteristics.

In healthy subjects, compared to overnight fasting, a high fat meal reduced brigatinib Cmax by 13% with no effect on AUC. Brigatinib can be administered with or without food (SmPC section 5.2). Brigatinib was moderately bound (91%) to human plasma proteins and binding was not concentration dependent. In patients given brigatinib 180 mg once daily, the geometric mean apparent volume of distribution (Vz/F) of brigatinib at steady state was 153 L, indicating moderate distribution into tissues.

The flat dose of 180 mg QD is appropriate for the expected weight range.

Pop PK analysis indicated that no dose adjustments are necessary in patients with either mild renal or hepatic impairment. No dose adjustment of Alunbrig is required for patients with mild hepatic impairment (Child-Pugh class A) or moderate hepatic impairment (Child-Pugh class B). A reduced starting dose of 60 mg once daily for the first 7 days, then 120 mg once daily is recommended for patients with severe hepatic impairment (Child-Pugh class C).

Creatinine clearance was not found to be a relevant covariate in the Pop PK analysis and no dose adjustment of brigatinib is required for patients with mild or moderate renal impairment (estimated glomerular filtration rate (eGFR) $\geq$ 30 mL/min). However, a clear trend is observed for a decrease in clearance and an increase in AUC for patients with mild and especially moderate renal impairment. A reduced starting dose of 60 mg once daily for the first 7 days, then 90 mg once daily is recommended for patients with severe renal impairment (eGFR < 30 mL/min) (see sections 4.2 and 5.2 of the SmPC). Patients with severe renal impairment should be closely monitored for new or worsening respiratory symptoms that may indicate ILD/pneumonitis (e.g., dyspnoea, cough, etc.) particularly in the first week (see section 4.2 of the SmPC).

The Population PK analysis identified body weight, age and albumin to have impact on the PK of brigatinib. Exposure is decreased in patients with high body weight and higher in patients with low body weight, but without a clinical relevant impact on safety or efficacy. The changes related to age and albumin are not considered to be clinically relevant. The limited data on the safety and efficacy of Alunbrig in patients aged 65 years and older suggest that a dose adjustment is not required in elderly patients. There are no available data on patients over 85 years of age (see sections 4.2 and 4.8).

Brigatinib is a substrate of the transporters P-gp and BCRP. P-gp is involved in the blood-brain barrier. No further in vivo studies have been conducted to investigate these transporters. One of the reasons is that the result of 123 reported digoxin DDI clinical studies [35] indicated that interactions of digoxin (the recommended P-gp substrate) with P-gp inhibitors are limited, i.e., P-gp inhibitors did not increase digoxin AUC or $C_{max.}$ In vitro studies have shown that brigatinib inhibits both P-gp and BCRP. However, given that brigatinib exhibits high solubility and high permeability, inhibition of P gp and BCRP is not expected to result in a clinically meaningful change in the systemic exposure of brigatinib. No dose adjustment is required for Alunbrig during coadministration with P gp and BCRP inhibitors.

Coadministration of brigatinib with substrates of P-gp, (e.g., digoxin, dabigatran, colchicine, pravastatin), BCRP (e.g., methotrexate, rosuvastatin, sulfasalazine), organic cation transporter 1

[35] Fenner KS, Troutman MD, Kempshall S, Cook JA, Ware JA, Smith DA, Lee CA. Drug-drug interactions mediated through P-glycoprotein: clinical relevance and in vitro-in vivo correlation using digoxin as a probe drug. Clin Pharmacol Ther. 2009 Feb;85(2):173-81. doi: 10.1038/clpt.2008.195.

(OCT1), multidrug and toxin extrusion protein 1 (MATE1), and 2K (MATE2K) may increase their plasma concentrations. Patients should be closely monitored when Alunbrig is coadministered with substrates of these transporters with a narrow therapeutic index (e.g., digoxin, dabigatran, methotrexate).

Brigatinib is metabolized mainly by CYP2C8 and CYP3A4. A clinical DDI study in healthy subjects has been conducted to investigate the effect of CYP3A/CYP2C8 inhibitors and CYP3A inducer to brigatinib PK.

Concomitant administration of brigatinib with a strong CYP3A4 inducer or a strong CYP3A4 inhibitor gave the expected results with decrease and increase respectively in PK exposure (Cmax and AUC).

The concomitant use of strong CYP3A inhibitors with Alunbrig, including but not limited to certain antivirals (e.g., indinavir, nelfinavir, ritonavir, saquinavir), macrolide antibiotics (e.g., clarithromycin, telithromycin, troleandomycin), antifungals (e.g., ketoconazole, voriconazole), mibefradil, and nefazodone should be avoided. If concomitant use of strong CYP3A inhibitors cannot be avoided, the dose of Alunbrig should be reduced by approximately 50% (i.e. from 180 mg to 90 mg, or from 90 mg to 60 mg). After discontinuation of a strong CYP3A inhibitor, Alunbrig should be resumed at the dose that was tolerated prior to the initiation of the strong CYP3A inhibitor (see sections 4.4 and 4.5 of the SmPC).

Moderate CYP3A inhibitors (e.g., diltiazem and verapamil) may increase the AUC of brigatinib by approximately 40% based on simulations from a physiologically-based pharmacokinetic model. No dose adjustment is required for Alunbrig in combination with moderate CYP3A inhibitors. Patients should be closely monitored when Alunbrig is coadministered with moderate CYP3A inhibitors (SmPC, section 4.5)..

Grapefruit or grapefruit juice may also increase plasma concentrations of brigatinib and should be avoided (see sections 4.2 and 4.5 of the SmPC).

The result of the study with the strong CYP2C8 inhibitor gemfibrozil together with PBPK modelling indicated that the effect of gemfibrozil on the pharmacokinetics of brigatinib is not clinically meaningful. No dose adjustment is required during coadministration with strong CYP2C8 inhibitors.

The concomitant use of strong CYP3A inducers with Alunbrig, including but not limited to rifampicin, carbamazepine, phenytoin, rifabutin, phenobarbital, and St. John's wort should be avoided (see sections 4.4 and 4.5 of the SmPC).

Moderate CYP3A inducers may decrease the AUC of brigatinib by approximately 50% based on simulations from a physiologically-based pharmacokinetic model. The concomitant use of moderate CYP3A inducers with Alunbrig, including but not limited to efavirenz, modafinil, bosentan, etravirine, and nafcillin should be avoided (see sections 4.2 and 4.5 of the SmPC).

In vitro studies in hepatocytes have shown that brigatinib is an inducer of CYP3A4. Clinical drug-drug interaction studies with CYP3A sensitive substrates have not been conducted. Brigatinib may reduce plasma levels of coadministered medicinal products that are predominantly metabolised by CYP3A. Therefore, coadministration of Alunbrig with CYP3A substrates with a narrow therapeutic index (e.g., alfentanil, fentanyl, quinidine, cyclosporine, sirolimus, tacrolimus) should be avoided as their effectiveness may be reduced.

Alunbrig may also induce other enzymes and transporters (e.g., CYP2C, P-gp) via the same mechanisms responsible for induction of CYP3A (e.g., pregnane X receptor activation).

A clinical DDI study in patients to evaluate the net effect of repeated dosing of brigatinib on the single-dose pharmacokinetics of the sensitive CYP3A substrate, **midazolam** is recommended.

Other TKIs have been associated with QT prolongation, and no thorough QT study has been conducted with brigatinib. ECG and exposure data are available from study AP26113-11-101 and no effect on ECG elements of significance was found. Few patients included in the ECG investigation have been dosed with the therapeutic dose.

Exposure-Response analyses were conducted as part of clinical studies 101 and 201. In general, no associations were observed between GeoMean trough brigatinib plasma concentrations and confirmed ORR or PFS in the two clinical studies. In addition, higher Ctrough was associated with a trend for higher probability of SAEs or Grade 2 or higher AEs.

2.5.5. Conclusions on clinical pharmacology

Overall, the clinical pharmacology of brigatinib has been adequately addressed in a structured and rationale designed clinical development program.

2.1. Clinical efficacy

The efficacy of brigatinib in the proposed indication is supported by three clinical studies, a phase 1/2 study (AP26113-11-101), and a pivotal phase 2 study (AP26113-13-201), and top-line results from a phase 3 study (AP 26113-13-301).

2.2. Dose response study

Study AP26113-11-101: A (study 101): A Phase 1/2 Study of the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-Tumor Activity of the Oral ALK/EGFR Inhibitor AP26113

This on-going open-label study was designed in two parts: a dose escalation phase using a 3+3 design to determine the recommended phase 2 dose (RP2D), followed by an expansion cohort. The initial dose escalation cohort included patients with advanced malignancies (other than leukaemia). Eligible patients were over 18 years of age, had measurable disease by RECIST v1.1, had ECOG performance status 0 or 1 and were refractory to available therapies. Daily doses of brigatinib were escalated from 30 mg to 300 mg orally. The expansion phase included mainly patients with ALK+ advanced NSCLC. The initial RP2D was 180 mg QD (see section on clinical pharmacology). However, based on safety findings of early onset pulmonary events (EOPEs), the 180 mg QD dose was not evaluated further. Instead, 90 mg QD and 90 mg QD for 7 days followed by escalation to 180 mg QD (90 /180 mg) were tested in the phase 2 portion. Overall response rate (ORR) by investigator assessment was the primary efficacy endpoint.

At the data cut-off of 31/05/2016, a total of 137 patients were enrolled and dosed. For the purpose of the analysis, dose groups were collapsed and data from dose escalation and expansion cohorts were combined. The study population included 79 patients with ALK+ NSCLC; the majority had been previously treated with crizotinib: 71/79. A total of 50 ALK+ NSCLC patients had brain metastases at baseline. The median duration of treatment for patients with ALK+ NSCLC was 20 months. The median age of ALK+ NSCLC patients in the study was 54 years. Females made up 49%. ECOG status was 0 for 34% and 1 for 65%. The majority (94%) had adenocarcinoma.

The 90 /180 mg group, corresponding to the proposed dose for this application, included 25 ALK+ NSCLC patients previously treated with crizotinib. In this group, 19/25 patients (76.0%; 95% CI 54.9%, 90.6%) had a confirmed objective response, of which 3/25 (12.0%; 95% CI: 2.5%, 31.2%) showed a confirmed complete response (CR). The median time to response was 1.9 months (range 1.2 – 6.0 months). The KM estimate median duration of response (n=19) was 26.1 months (95% CI:

7.9, 26.1). The KM estimate of median PFS was 16.3 months (95% CI: 9.2, not reached). Median overall survival (KM estimate) was not reached.

Table 28: Response by Collapsed Dose Group: ALK+ NSCLC Patients with Prior Treatment with Crizotinib

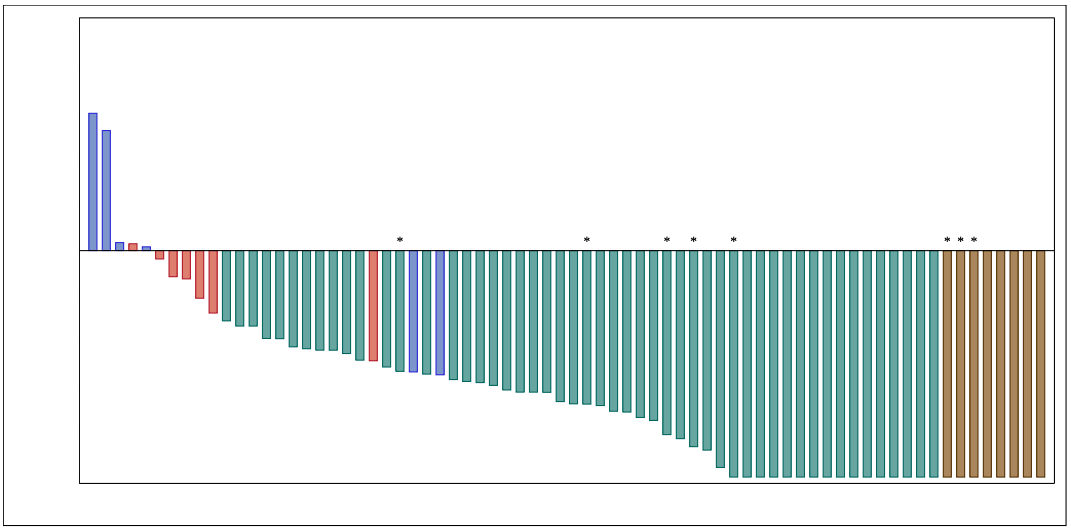
Response	30 mg QD/ 60 mg QD N=1	90 mg QD N=13	120 mg QD/ 60 mg BID N=5	90 mg QD → 180 mg QD[a] N=25	180 mg QD/ 90 mg BID N=23	240 mg QD/ 300 mg QD/ 120 mg BID N=4	Total Patients N=71
Confirmed + Unconfirmed ORR							
n (%)	1 (100.0%)	10 (76.9%)	3 (60.0%)	20 (80.0%)	15 (65.2%)	2 (50.0%)	51 (71.8%)
95% CI	2.5%, 100.0%	46.2%, 95.0%	14.7%, 94.7%	59.3%, 93.2%	42.7%, 83.6%	6.8%, 93.2%	59.9%, 81.9%
Complete Response [a]							
n (%)	0	0	0	3 (12.0%)	2 (8.7%)	0	5 (7.0%)
95% CI	NA	NA	NA	2.5%, 31.2%	1.1%, 28.0%	NA	2.3%, 15.7%
Partial Response							
n (%)	1 (100.0%)	10 (76.9%)	3 (60.0%)	17 (68.0%)	13 (56.5%)	2 (50.0%)	46 (64.8%)
95% CI	2.5%, 100.0%	46.2%, 95.0%	14.7%, 94.7%	46.5%, 85.1%	34.5%, 76.8%	6.8%, 93.2%	52.5%, 75.8%
Confirmed ORR							
n (%)	0	7 (53.8%)	3 (60.0%)	19 (76.0%)	14 (60.9%)	1 (25.0%)	44 (62.0%)
95% CI	NA	25.1%, 80.8%	14.7%, 94.7%	54.9%, 90.6%	38.5%, 80.3%	0.6%, 80.6%	49.7%, 73.2%
Stable Disease (Best Response)							
n (%)	0	0	0	2 (8.0%)	3 (13.0%)	2 (50.0%)	7 (9.9%)
95% CI	NA	NA	NA	1.0%, 26.0%	2.8%, 33.6%	6.8%, 93.2%	4.1%, 19.3%
Non–Complete Response/Non–Progressive Disease[b]							
n (%)	0	3 (23.1%)	1 (20.0%)	0	0	0	4 (5.6%)
95% CI	NA	5.0%, 53.8%	0.5%, 71.6%	NA	NA	NA	1.6%, 13.8%
Disease Control Rate							
n (%)	1 (100.0%)	13 (100.0%)	4 (80.0%)	22 (88.0%)	18 (78.3%)	4 (100.0%)	62 (87.3%)
95% CI	2.5%, 100.0%	75.3%, 100.0%	28.4%, 99.5%	68.8%, 97.5%	56.3%, 92.5%	39.8%, 100.0%	77.3%, 94.0%
Progressive Disease (Best Response)							
n (%)	0	0	0	2 (8.0%)	5 (21.7%)	0	7 (9.9%)
95% CI	NA	NA	NA	1.0%, 26.0%	7.5%, 43.7%	NA	4.1%, 19.3%

Source: Table 14.2.5.1 (Data Extraction Date: 31 May 2016)

[a] All complete responses were confirmed.

[b] Non-CR/non-PD is included because 3 patients were enrolled without measureable disease at baseline; these patients are included in the DCR.

Abbreviations: ALK+ = anaplastic lymphoma kinase-positive, ORR = objective response rate; NA = not applicable, NSCLC = non-small cell lung cancer



Source: Figure 14.2.12.1.1, (Data Extraction Date: 31 May 2016), Study AP26113-11-101 CSR. Note: N=72; 7 patients either did not have measurable disease at baseline (n=4) or did not have an on-study target lesion assessment prior to first assessment of PD (n=3). [a]Crizotinib-naïve patients

Figure 15: Investigator-Assessed Best Percent Change from Baseline of Target Lesion Sum Diameter: ALK+ NSCLC Patients

In the 90/180 mg QD group of ALK+ advanced NSCLC, there were 18 evaluable patients with brain metastases at baseline (all previously exposed to crizotinib), of which 8 (44.4%; 95% CI: 21.5%, 69.2%) had a confirmed response, and 7 (38.9%; 95% CI: 17.3%, 64.3%) had a CR (not confirmed). The KM estimate median intracranial duration of response was 11.4 months (95% CI: 5.6, 11.4) and the KM estimate median intracranial PFS was not reached.

2.2.1. Main study

Study AP26113-13-201: A Randomized Phase 2 Study of AP26113 in Patients with ALK-positive, Non-small Cell Lung Cancer (NSCLC) Previously Treated with Crizotinib

Methods

This was a phase 2, open-label, randomized, multicentre, international study of the efficacy and safety of brigatinib in patients with advanced ALK+ NSCLC previously treated with crizotinib. All patients were randomized to one of two regimens of brigatinib until disease progression or intolerable toxicity. There was no placebo or active control arm.

After end of treatment, or in the event of premature discontinuation, patients were followed up every 3 months (e.g. for survival and subsequent anticancer therapy) for 2 years after the last patient enrolled in the study.

Study Participants

Inclusion criteria:

1. Histologically or cytologically confirmed locally advanced or metastatic NSCLC that was ALK+.

2. Met one of the following two criteria:

    a. Documented ALK rearrangement by a positive result from the Vysis® ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit; or

b. Documented ALK positivity by a different test and tissue available for the Vysis FISH test. Tissue was derived preferably from a biopsy taken after progression with crizotinib. If such a sample was not available, testing could have been performed with archived tumor tissue.

3. Progressive disease while on crizotinib, as assessed by the investigator or treating physician.

4. Had at least 1 measurable lesion per RECIST v1.1.

5. Recovered from toxicities related to prior anticancer therapy to National Cancer Institute (NCI US) Common Terminology Criteria for Adverse Events (CTCAE, v4.0) grade ≤2.

6. Was a male or female patient ≥18 years old.

7. Had a life expectancy ≥3 months.

8. Had adequate organ and hematologic function, as determined by:

a. Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤2.5× upper limit of normal (ULN; ≤5× ULN was acceptable if liver metastases were present);

b. Total serum bilirubin ≤1.5× ULN (<3.0× ULN for patients with Gilbert syndrome);

c. Serum creatinine ≤1.5× ULN;

d. Serum lipase/amylase ≤1.5× ULN;

e. Absolute neutrophil count (ANC) ≥1500/μL;

f. Platelets ≥75000/μL;

g. Haemoglobin ≥10 g/dL.

9. ECOG performance status ≤2 (refer to Appendix B of the protocol in Appendix 16.1.1).

10. Normal QT interval (QT) on screening ECG evaluation.

11. For female patients of childbearing potential, a negative pregnancy test must have been documented prior to enrollment.

12. Female and male patients who were fertile must have agreed to use a highly effective form of contraception with their sexual partners throughout study participation.

13. Signed and dated informed consent indicating that the patient had been informed of all pertinent aspects of the study, including the potential risks, and was willingly participating.

14. Willingness and ability to comply with scheduled visits and study procedures.

Exclusion Criteria:

1. Received any prior ALK-targeted TKI other than crizotinib.

2. Received crizotinib within 3 days of the first dose of brigatinib (Day 1, Cycle 1).

3. Received cytotoxic chemotherapy, investigational agents, or radiation within 14 days, except SRS or stereotactic body radiosurgery.

4. Received monoclonal antibodies or had major surgery within 30 days of the first dose of brigatinib (Day 1, Cycle 1).

5. Diagnosed with another primary malignancy within the past 3 years (except for adequately treated non-melanoma skin cancer, cervical cancer in situ, or prostate cancer, which were allowed within 3 years).

6. Symptomatic CNS metastases that were neurologically unstable or required an increasing dose of corticosteroids.

7. Current spinal cord compression.

8. Significant, uncontrolled, or active cardiovascular disease.

9. History or the presence of pulmonary interstitial disease or drug-related pneumonitis.

10. Ongoing or active infection.

11. Known history of human immunodeficiency virus (HIV).

12. History of or active significant GI bleeding within 3 months of the first dose of brigatinib.

13. Known or suspected hypersensitivity to brigatinib or its excipients.

14. Malabsorption syndrome or other GI illness that could affect oral absorption of the study drug.

15. Any condition or illness that, in the opinion of the investigator, would compromise patient safety or interfere with evaluation of the drug study.

16. Pregnant or breastfeeding.

Treatments

Patients were randomized 1:1 to receive brigatinib 90 mg QD (Arm A) or 90/180 mg QD (i.e. 90 mg QD for 7 days then 180 mg QD) (Arm B). A cycle comprised 28 days of treatment. Brigatinib was taken orally with 240 mL of water, with or without food.

Patients were dosed with brigatinib until disease progression or intolerable toxicity. Treatment could be continued after progression, at the discretion of the investigator. Patients allocated to the 90 mg QD group could be escalated to 180 mg QD at progression.

The drug product was supplied as 30 mg tablets (formulation 3).

Palliative and supportive care was permitted during the study. However anticancer therapy or extensive surgery was prohibited for the duration of the study. Patients with CNS lesions requiring stereotactic radiosurgery (SRS) were allowed to continue study drug after appropriate interruption, as determined by the investigator; however, for analysis purposes, these patients were considered to have progressive disease (PD).

Objectives

The primary objective was to determine the efficacy of brigatinib, as evidenced by confirmed ORR (by investigator), in patients with ALK+ locally advanced or metastatic NSCLC whose disease has progressed on therapy with crizotinib.

The secondary objectives were:

- To further characterize the efficacy of brigatinib in patients with ALK+, locally advanced or metastatic NSCLC whose disease has progressed on therapy with crizotinib, as shown by disease control rate, time to response, duration of response, PFS, OS, and time on treatment.
- To assess CNS response and PFS, per RECIST v1.1, in those patients who had active brain metastases.
- To assess the safety and tolerability of brigatinib in study patients.

- To measure steady state plasma levels of brigatinib for use in population PK modelling.
- To assess patient-reported symptoms and health-related quality-of-life (HRQoL) with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30 (v3.0).

Exploratory objectives were:

- Correlation of brigatinib exposure with both efficacy and safety.
- Correlation of tumour and plasma biomarkers with brigatinib efficacy and safety.

Outcomes/endpoints

The primary endpoint, confirmed ORR assessed by the investigator, was defined as the proportion of patients who were confirmed to have achieved CR or PR, as determined per RECIST v1.1; confirmed responses were those that persisted on repeat imaging 4 weeks or more after initial response.

Secondary efficacy endpoints were as follows:

- Confirmed ORR assessed by IRC.
- For randomized patients with active brain metastases at enrollment:
    - intracranial ORR as evaluated by IRC
    - intracranial PFS as evaluated by IRC
- Time to response
- Duration of response
- Time on treatment
- Disease control rate
- PFS
- OS
- Patient-Reported Symptoms of Lung Cancer and HRQoL assessed by administering the EORTC QLQ-C30 (v3.0) questionnaire at screening and every 4 weeks thereafter.

Sample size

Assuming that the true ORR is 35% a total of 109 subjects in each treatment regimen is needed in order to have approximately 90% power to rule out the uninteresting rate of 20% at a two-sided alpha level of 0.025 using exact binomial test.

Randomisation

Patients were allocated in a 1:1 ratio to each dosing regimen (Arm A and Arm B) in a randomized manner, and with two stratification factors:

- Brain metastases at baseline (present vs absent)
- Best response to prior crizotinib therapy as assessed by the investigator (complete response [CR] or partial response [PR] vs any other response or status unknown)

Blinding (masking)

The study was open-label.

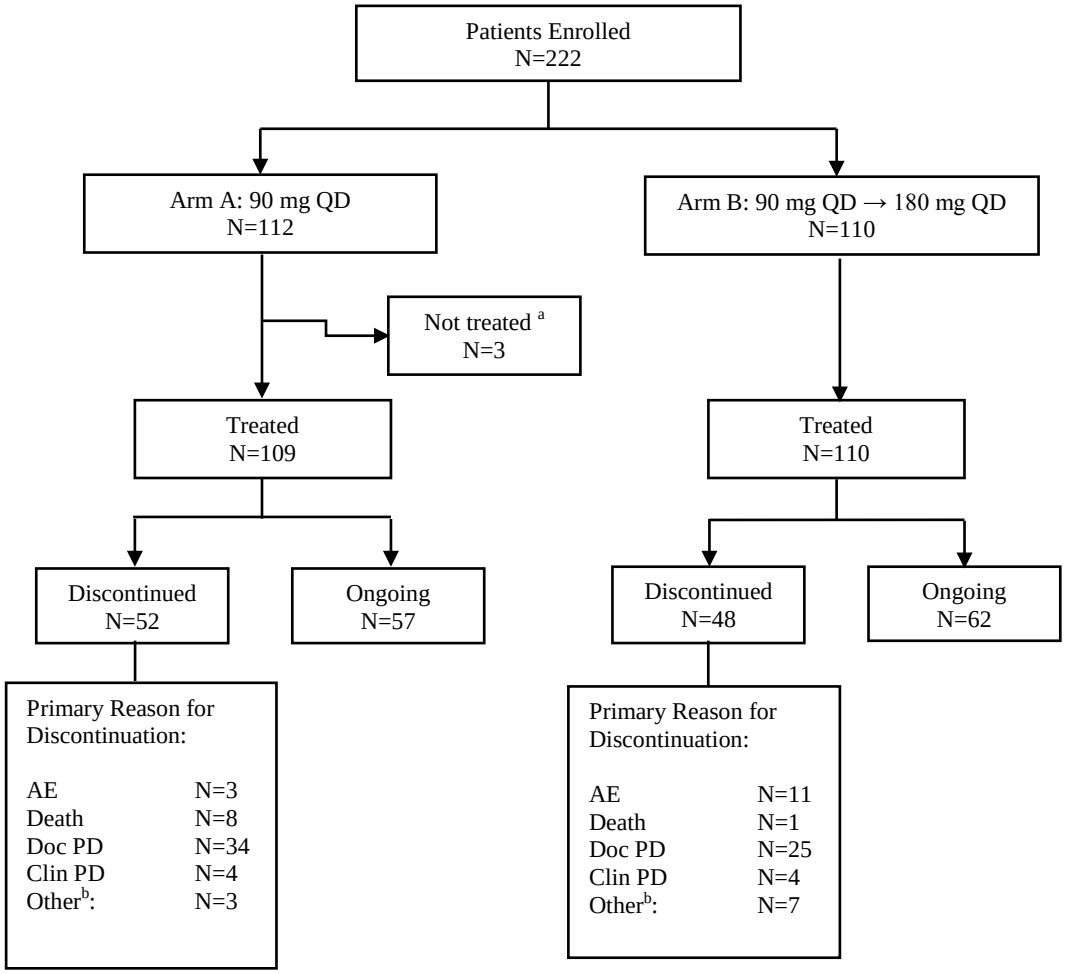
Statistical methods

The primary endpoint was ORR and the 95%/97.5% confidence intervals were calculated as exact 2-sided binomial confidence intervals. The study was considered to have achieved the primary endpoint, if the ORR was shown to be significantly higher than 20% at a two-sided alpha level of 0.025 at the final analysis for that regimen.

Patients were stratified at randomisation by brain metastases at baseline (present vs absent) and best prior response to crizotinib therapy (CR or PR vs any other response or status unknown).

Results

Participant flow



A total of 268 patients were screened in Study AP26113-13-201. Of those, 222 patients were randomized and 46 were excluded. In 4 patients, the reason for screen-failure was not reported. In the remaining 42 patients, the reasons for exclusion were as follows (in some cases, patients had more than one reason for exclusion).

Table 29: Reasons for Exclusion

Reason for Exclusion	Number of Patients Excluded for this Reason
Did not have serum lipase/amylase ≤1.5×ULN (Inclusion Criterion #10d)	6
Did not have willingness and ability to comply with scheduled visits and study procedures (Inclusion Criterion #16)	6
Did not have life expectancy ≥3 months (Inclusion Criterion #9)	5
Did not have at least 1 measurable lesion per RECIST v1.1 (Inclusion Criterion #5)	5
Had symptomatic or neurologically unstable CNS metastases that require an increasing dose of corticosteroids (Exclusion Criterion #6)	5
Did not have ECOG performance status ≤2 (Inclusion Criterion #11)	4
Did not have a normal QT interval on screening ECG evaluation (Inclusion Criterion #12)	4
Had an ongoing or active infection (Exclusion Criterion #10)	4
Did not have progressive disease while on crizotinib (Inclusion Criterion #3)	2
Had a history or the presence of pulmonary interstitial disease or drug-related pneumonitis (Exclusion Criterion #9)	2
Had any condition or illness that, in the opinion of the investigator would compromise patient safety or interfere with evaluation of the stud drug (Exclusion Criterion #15)	2
Did not have ALT/AST ≤2.5×ULN (or ≤5×ULN if liver metastases are present) (Inclusion Criterion #10a)	1
Did not have ANC >1500/µL (Inclusion Criterion #10e)	1
Did not have hemoglobin >10g/dL (Inclusion Criterion #10g)	1
Had not recovered from toxicities related to prior anticancer therapy to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, v4.0) grade ≤2 (Inclusion Criterion #7)	1
Received any prior ALK-targeted TKI other than crizotinib (Exclusion Criterion #1)	1
Received crizotinib within 3 days of the first dose of brigatinib (Day 1, Cycle 1) (Exclusion Criterion #2)	1
Received cytotoxic chemotherapy, investigational agents or radiation within 14 days, except SRS or stereotactic body radiosurgery (Exclusion Criterion #3)	1

Recruitment

Seventy-one investigational sites in 18 countries enrolled 222 patients into the study from the following regions: Asian Pacific region (68 patients), Europe (105 patients), and North America (49 patients). The study is ongoing. The last patient was randomized on 21/09/2015.

Conduct of the study

Protocol amendments:

The original protocol (dated 27 June 2013) was amended twice, with an additional third amendment applicable only to South Korea.

Protocol amendment 1 (dated 03 February 2014) made the following key changes to the original protocol.

- Adjusted the study design to allow for randomization into two different study arms, each with a different dosing regimen (90 mg QD or 180 mg QD with a 7-day lead-in at 90 mg QD).
- Increased enrolment projections to fill both study arms (and added at least 6 more months to accrue patients).
- Updated the statistical testing methods to address both study arms.
- Updated the clinical summary of data from the phase 1/2 study of brigatinib, including an assessment of the respiratory events and reports of early onset pulmonary syndrome.
- Updated the sections describing sampling for molecular genetic testing to allow for analysis of various tumour and plasma biomarkers as is feasible at different sites.

- Modified the wording of protocol eligibility criteria to further clarify the type of patients to be enrolled.

Protocol deviations: There were 42 protocol deviations considered by the Sponsor as major (e.g. involving inclusion or exclusion criteria, prohibited concomitant medication).

Baseline data

Table 30: Demographics (ITT Population)

	Arm A 90 mg QD N=112	Arm B 90 mg QD →180 mg QD N=110	Total N=222
Demographics			
Sex, n (%)			
Female	62 (55.4)	64 (58.2)	126 (56.8)
Male	50 (44.6)	46 (41.8)	96 (43.2)
Age (years)			
N	112	110	222
Mean (Std)	51.5 (13.01)	55.5 (12.96)	53.4 (13.11)
Median	50.5	56.5	54.0
Min, Max	18, 82	20, 81	18, 82
Age Category, n (%)			
18-49 years	50 (44.6)	33 (30.0)	83 (37.4)
50-64 years	40 (35.7)	47 (42.7)	87 (39.2)
65-74 years	20 (17.9)	23 (20.9)	43 (19.4)
≥75 years	2 (1.8)	7 (6.4)	9 (4.1)
Race, n (%)			
White	72 (64.3)	76 (69.1)	148 (66.7)
Black or African American	1 (0.9)	2 (1.8)	3 (1.4)
Asian	39 (34.8)	30 (27.3)	69 (31.1)
Unknown	0	2 (1.8)	2 (0.9)
Ethnicity, n (%)			
Hispanic or Latino	5 (4.5)	8 (7.3)	13 (5.9)
Not Hispanic or Latino	107 (95.5)	102 (92.7)	209 (94.1)

Source: Table 14.1.2.1 (Data Extraction Date: 31 May 2016)
Abbreviations: Max = maximum; Min = minimum; n = number; QD = once daily; Std = standard deviation

Table 31: Baseline Disease Characteristics: ITT Population (Study AP26113-13-201)

	Arm A 90 mg QD N=112	Arm B 90 mg QD →180 mg QD N=110	Total Patients N=222
Prior Cigarette Smoking History, n (%)			
Never	71 (63.4)	63 (57.3)	134 (60.4)
Current	6 (5.4)	4 (3.6)	10 (4.5)
Former	34 (30.4)	43 (39.1)	77 (34.7)
Unknown	1 (0.9)	0	1 (0.5)
ECOG Performance Status, n (%)			
0	34 (30.4)	45 (40.9)	79 (35.6)
1	71 (63.4)	56 (50.9)	127 (57.2)
2	7 (6.3)	9 (8.2)	16 (7.2)
ALK+ by Vysis FISH (locally or centrally)[a] n (%)			
Yes	99 (88.4)	98 (89.1)	197 (88.7)
No (central test not performed or negative)	13 (11.6)	12 (10.9)	25 (11.3)
Stage at Study Entry, n (%)			
IIIA	0	1 (0.9)	1 (0.5)
IIIB	3 (2.7)	1 (0.9)	4 (1.8)
IV	109 (97.3)	108 (98.2)	217 (97.7)
Time since Initial Diagnosis (months)			

	Arm A 90 mg QD N=112	Arm B 90 mg QD →180 mg QD N=110	Total Patients N=222
N	110	110	220
Mean (SD)	32.7 (28.84)	36.6 (42.14)	34.6 (36.08)
Median	21.6	24.1	23.9
Min, Max	2, 146	3, 310	2, 310
Histopathological NSCLC Classification, n (%)			
Adenocarcinoma	107 (95.5)	108 (98.2)	215 (96.8)
Adenosquamous carcinoma	1 (0.9)	0	1 (0.5)
Squamous	2 (1.8)	1 (0.9)	3 (1.4)
Large cell	1 (0.9)	1 (0.9)	2 (0.9)
Mucoepidermoid carcinoma	1 (0.9)	0	1 (0.5)
Brain Metastases at Study Entry, n (%)	80 (71.4)	74 (67.3)	154 (69.4)
Active[b] Brain Metastases at Study Entry, n/N (%)	54/80 (67.5)	55/74 (74.3)	109/154 (70.8)
Systemic Metastases at Study Entry, n (%)			
Liver Metastases	34 (30.4)	23 (20.9)	57 (25.7)
Bone Metastases	50 (44.6)	37 (33.6)	87 (39.2)
Lung Metastases	94 (83.9)	93 (84.5)	187 (84.2)
Most Recent Systemic Therapy, n (%)			
Crizotinib	107 (95.5)	106 (96.4)	213 (95.9)
Chemotherapy	5 (4.5)	4 (3.6)	9 (4.1)
Best Response to Prior Crizotinib Regimen(s), n (%)			
Complete Response	5 (4.5)	2 (1.8)	7 (3.2)
Partial Response	65 (58.0)	70 (63.6)	135 (60.8)
Stable Disease	28 (25.0)	21 (19.1)	49 (22.1)
Progressive Disease	8 (7.1)	6 (5.5)	14 (6.3)
Other[c]	1 (0.9)	1 (0.9)	2 (0.9)
Unknown	5 (4.5)	10 (9.1)	15 (6.8)
Any Prior Chemotherapy, n (%)			
Yes	83 (74.1)	81 (73.6)	164 (73.9)
No	29 (25.9)	29 (26.4)	58 (26.1)
Number of Prior Systemic Anti-cancer Regimens, n (%)			
1 regimen	29 (25.9)	27 (24.5)	56 (25.2)
2 regimen	40 (35.7)	45 (40.9)	85 (38.3)
≥3 regimen	43 (38.4)	38 (34.5)	81 (36.5)
Prior Platinum-based Chemotherapy, n (%)			
Yes	83 (74.1)	80 (72.7)	163 (73.4)
No	29 (25.9)	30 (27.3)	59 (26.6)
Prior Radiation Therapy, n (%)			
Yes	68 (60.7)	58 (52.7)	126 (56.8)
No	44 (39.3)	52 (47.3)	96 (43.2)

Source: Table 14.1.2.2 (Data Extraction Date: 31 May 2016), Study AP26113-13-201 CSR. Abbreviations: ALK+ = anaplastic lymphoma kinase – positive; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence imaging in situ hybridization; ITT = Intent-to-treat; Max = maximum; Min = minimum; n = number; NSCLC = non-small cell lung cancer; PR = partial response; QD = once daily; SD = standard deviation. [a]Of the 24 patients without a positive local or central ALK Vysis FISH test result: no central test result was due to insufficient tissue (n=6) or improper tissue preparations (n=12); central test negative (n=5); and central test abnormal – loss of 3' ALK signal (n=1). [b]An active brain lesion is defined for the purpose of this study as a lesion that has not previously been irradiated, or having had prior radiation treatment but then having definitely progressed after being irradiated. [c] Category of Other includes two patients (Patient 608-002 and Patient 624-004) for whom a response of PR or better was achieved but the exact classification was unknown.

Numbers analysed

Efficacy analyses were performed on the ITT population of 222 patients (i.e. all patients randomized to each regimen were analysed according to randomized allocation). Sensitivity analyses were conducted using the per-protocol population, which excluded 33 patients (22 without confirmed baseline ALK rearrangement by Vysis FISH test). The median follow-up time at the time of data extraction (31/05/2016) was 10.8 months.

Table 32: Patient Disposition (ITT Population)

	Arm A 90 mg QD N = 112	Arm B 90 mg QD→ 180 mg QD N = 110	Total N = 222
Treated patients, n (%)	109 (97.3)	110 (100.0)	219 (98.6)
Treatment ongoing	27 (24.1)	32 (29.1)	59 (26.6)
Treatment discontinued	82 (73.2)	78 (70.9)	160 (72.1)
Primary reason for discontinuation, n (%)			
Documented progressive disease (RECIST v1.1)	54 (48.2)	45 (40.9)	99 (44.6)
Clinical progressive disease	7 (6.3)	11 (10.0)	18 (8.1)
Adverse event	4 (3.6)	12 (10.9)	16 (7.2)
Death	10 (8.9)	1 (0.9)	11 (5.0)
Noncompliance with study drug	0 (0.0)	1 (0.9)	1 (0.5)
Physician decision	3 (2.7)	3 (2.7)	6 (2.7)
Withdrawal by subject	4 (3.6)	5 (4.5)	9 (4.1)
Randomized but never treated, n (%)	3 (2.7)	0 (0.0)	3 (1.4)
Follow-up (months)			
Median	19.56	24.26	22.87
Minimum, maximum	0.1, 35.2	0.1, 39.2	0.1, 39.2

Source: Table 14.1.1.1.
Abbreviations: ITT, intent to treat; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.
90 mg QD→180 mg QD = 90 mg QD for 7 days, followed by continuous dosing at 180 mg QD.

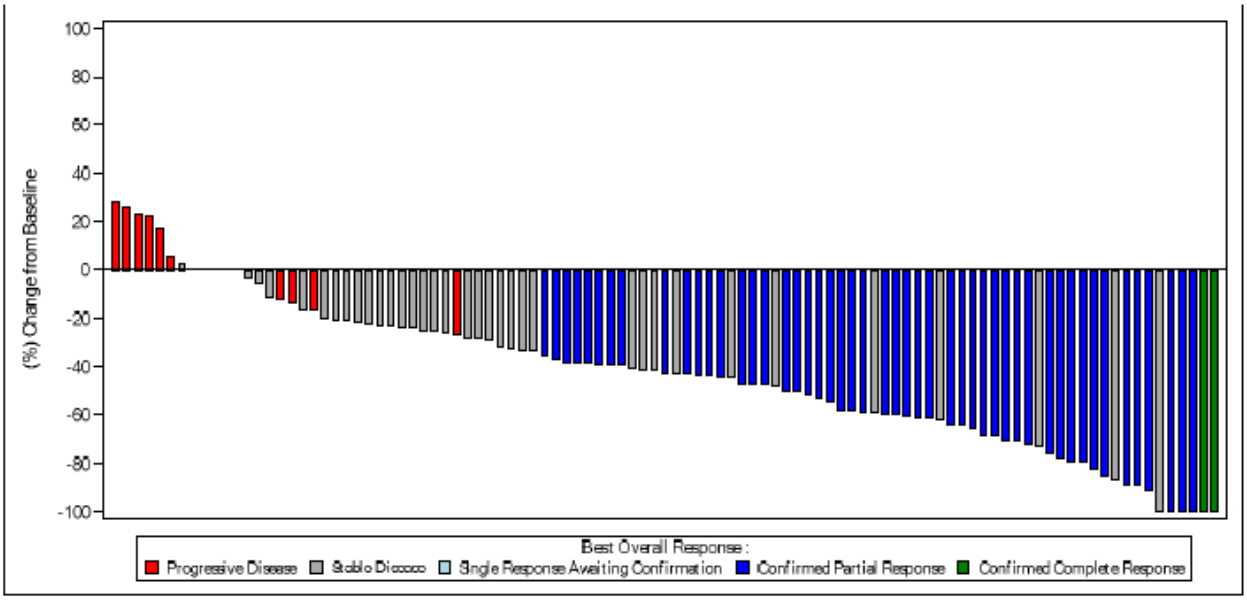
Outcomes and estimation

Primary endpoint: ORR assessed by the investigator

Table 33: Summary of Investigator-Assessed and IRC-Assessed Objective Responses: ITT Population (cutoff: 29Sept2017)

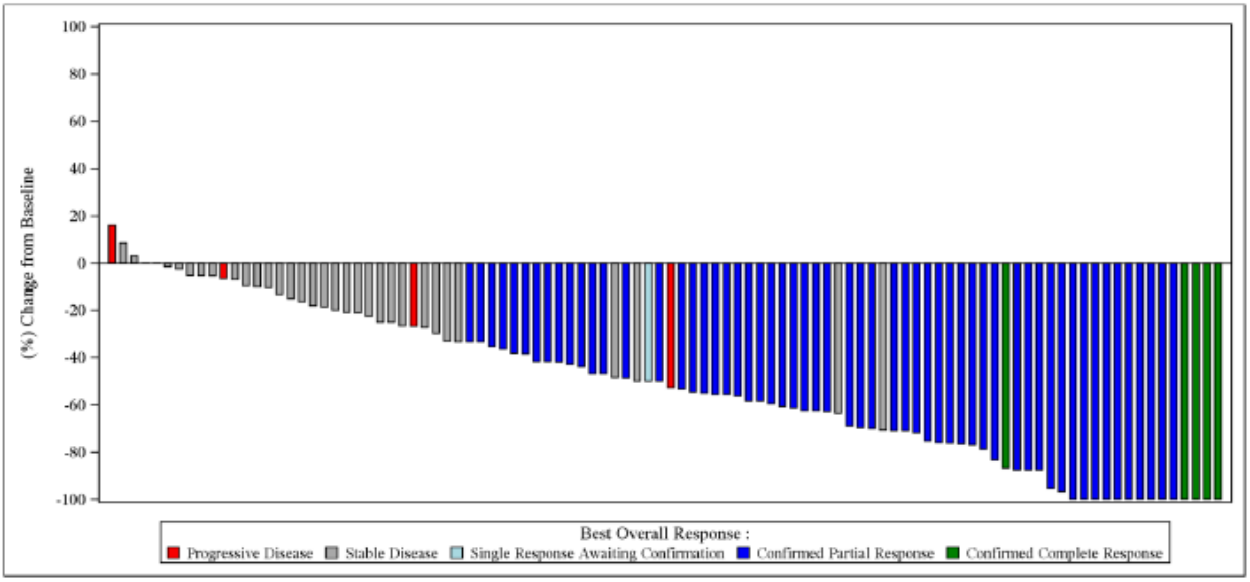
	Investigator Assessed		IRC Assessed [c]	
	Arm A 90 mg QD (N = 112)	Arm B 90 mg QD→ 180 mg QD (N = 110)	Arm A 90 mg QD (N = 112)	Arm B 90 mg QD→ 180 mg QD (N = 110)
Confirmed ORR, n (%) [a]	51 (45.5)	62 (56.4)	57 (50.9)	62 (56.4)
97.5%/95% CI [b]	(34.8-56.5)	(45.2-67.0)	(41.3-60.5)	(46.6-65.8)
Complete response, n (%)	2 (1.8)	5 (4.5)	6 (5.4)	6 (5.5)
Partial response, n (%)	49 (43.8)	57 (51.8)	51 (45.5)	56 (50.9)

Source: Table 14.2.1.1 and 14.2.3.1.
Abbreviations: IRC, independent review committee; ORR, objective response rate; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.
90 mg QD→180 mg QD = 90 mg QD for 7 days, followed by continuous dosing at 180 mg QD.
[a] Confirmed ORR is defined as the proportion of patients who achieved confirmed complete response or partial response per RECIST v1.1.
[b] The 95% and 97.5% CIs were calculated using the exact binomial method. The 97.5% CI is shown for the investigator-assessed ORR, and the 95% CI is shown for the IRC-assessed ORR.
[c] IRC last scan date: 07 September 2017.



Source: Figure 14.2.1.4.
Abbreviations: ITT, intent to treat.
Patients were considered evaluable if they had a nonmissing best percentage change from baseline in their target lesion sum. In this analysis, 101 of 112 patients had nonmissing data.

Figure 16: Waterfall Plot of investigator-assessed Best Percent Change in Target Lesion Sum Diameter: Arm A, 90 mg QD (cutoff: 29Sept2017)



Source: Figure 14.2.1.5.
Abbreviations: ITT, intent to treat.
Patients were considered evaluable if they had a nonmissing best percentage change from baseline in their target lesion sum. In this analysis, 100 of 110 patients had nonmissing data.

Figure 17: Waterfall Plot of investigator-assessed Best Percent Change in Target Lesion Sum Diameter: Arm B, 90 mg QD (cutoff: 29Sept2017)

Based on earlier cut-off date (31 May2016), the overall discordance rate for investigator-assessed ORR compared with IRC-assessed ORR of all patients was 18.8% (21/112) for Arm A and 19.1% (21/110) for Arm B

Table 34: Discordance of Investigator-Assessed and IRC-Assessed Systemic Confirmed Objective Response by Treatment Arm ITT Population (cutoff: 31May2016)

	ARM A (90 MG) (N=112)	ARM B (90/180 MG) (N=110)	Total (N=222)
Investigator-Assessed ORR, n (%)	50 (44.6%)	60 (54.5%)	110 (49.5%)
IRC-Assessed ORR, n (%)	55 (49.1%)	59 (53.6%)	114 (51.4%)
Overall Discordance Rate, n (%)	21 (18.8%)	21 (19.1%)	42 (18.9%)
Investigator Responder Versus IRC Non-Responder, n (%)	8 (7.1%)	11 (10.0%)	19 (8.6%)
IRC Responder Versus Investigator Non-Responder, n (%)	13 (11.6%)	10 (9.1%)	23 (10.4%)

Subgroup analyses

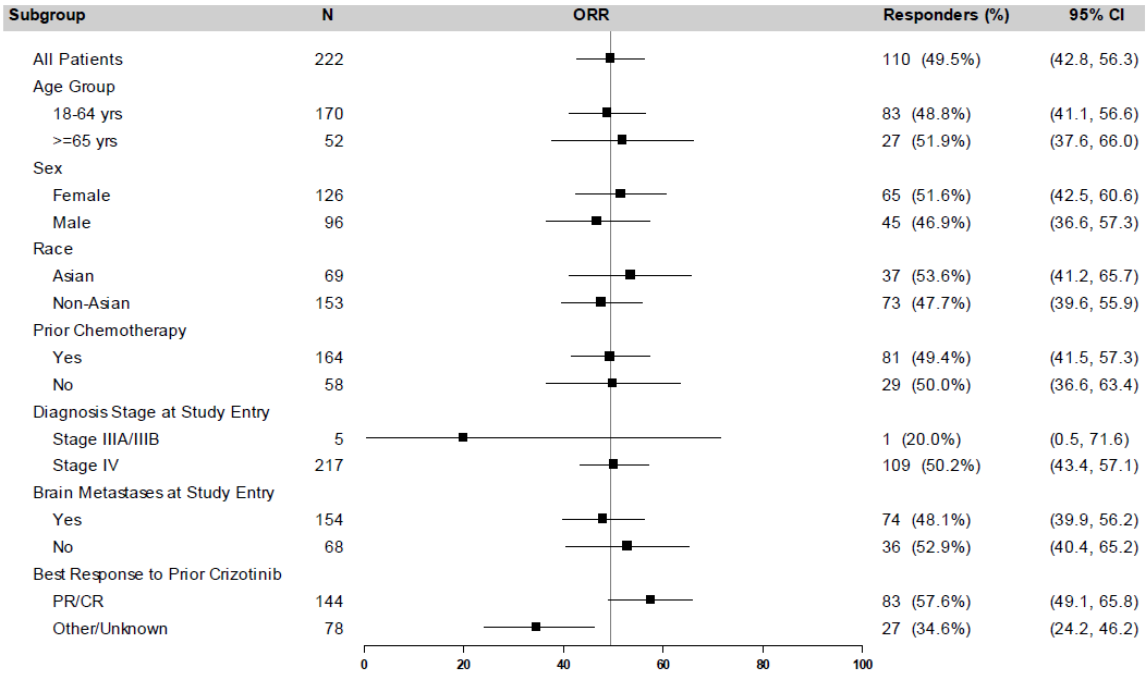


Figure 15: Confirmed Objective Response Rate by Subgroups: ITT Population (cutoff: 31May2016)

Secondary endpoints:

Time to Response

The median time to response among patients with investigator-assessed, confirmed ORR was 1.8 months (range: 1.7–7.3) for the 90 mg group and 1.9 months (range: 1.0–11.0) for the 90/180 mg group. For IRC-assessed response, the respective medians were 1.8 months (range: 1.6-7.3) and 1.9 months (range: 1.0-9.3).

Duration of response

The KM estimate median investigator-assessed duration of response was 12.0 months (95% CI: 7.4, not reached) for patients in the 90 mg group and 13.8 months (95% CI: 9.2, not reached) for patients in 90/180 mg group. The KM estimate median IRC-assessed duration of response was 16.4 months (95% CI, 7.4-24.9) for patients in the 90 mg group Arm A and 15.7 months (95% CI, 12.8-21.8) for patients in 90/180 mg group.

Responses in Patients with Brain Metastases at Baseline

IRC assessments of intracranial ORR and duration of intracranial response in patients from ALTA with measurable brain metastases (≥ 10 mm in longest diameter) at baseline are summarised in Table 5.

Table 35: Intracranial efficacy in patients with measurable brain metastases at baseline (cutoff: 29Sept2017)

IRC-assessed efficacy parameter	Patients with measurable brain metastases at baseline	
	90 mg regimen* (N = 26)	180 mg regimen† (N = 18)
Intracranial objective response rate		
(%)	50%	67%
95% CI	(30, 70)	(41, 87)
Intracranial disease control rate		
(%)	85%	83%
95% CI	(65, 96)	(59, 96)
Duration of intracranial response‡,		
Median (months)	9.4	16.6
95% CI	(3.7, 24.9)	(3.7, NE)

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

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

The KM median duration of intracranial response for patients with measurable brain metastases at baseline was 9.4 months (95% CI, 3.7-24.9) in the 90 mg arm and was 16.6 months (95% CI, 3.7-NR) in the 180 mg arm. For both arms, respectively, 61.5% (8 of 13) and 41.7% (5 of 12) of responders had an event.

The median time to intracranial response among patients with confirmed intracranial ORR was 1.8 months (range: 1.6–9.2) for Arm A (n=12) and 1.8 months (range: 1.6–2.3) for Arm B (n=12) for patients with measurable brain metastases.

The KM estimated median intracranial PFS for patients with measurable brain metastases at baseline was 11.1 months (95% CI, 5.6-23.7) for patients in the 90 mg arm (11 events, 26 patients [42.3%]) and 18.5 months (95% CI, 4.9-NR) for patients in the 180 mg arm (7 events, 18 patients [38.9%]).

Only Nonmeasurable Brain Metastases:

A confirmed CR was observed in 9.1% (5 of 55) of patients in the 90 mg arm and 17.9% (10 of 56) of patients in the 180 mg arm. The intracranial disease control rate was 81.8% (27 of 33) of patients in the 90 mg arm and 88.9% (32 of 36) of patients in the 180 mg arm. The median time to intracranial ORR among patients with confirmed intracranial response was 4.6 months (range: 3.5-7.4) for the 90 mg arm (n=4) and 2.4 months (range: 1.6-3.8) for the 180 mg arm (n=10).

Nonmeasurable and Active Brain Metastases:

It is possible that response could be affected by previous irradiation of CNS metastases, including pseudoprogression and therefore intracranial response according to history of CNS irradiation was requested and are presented in the below table.

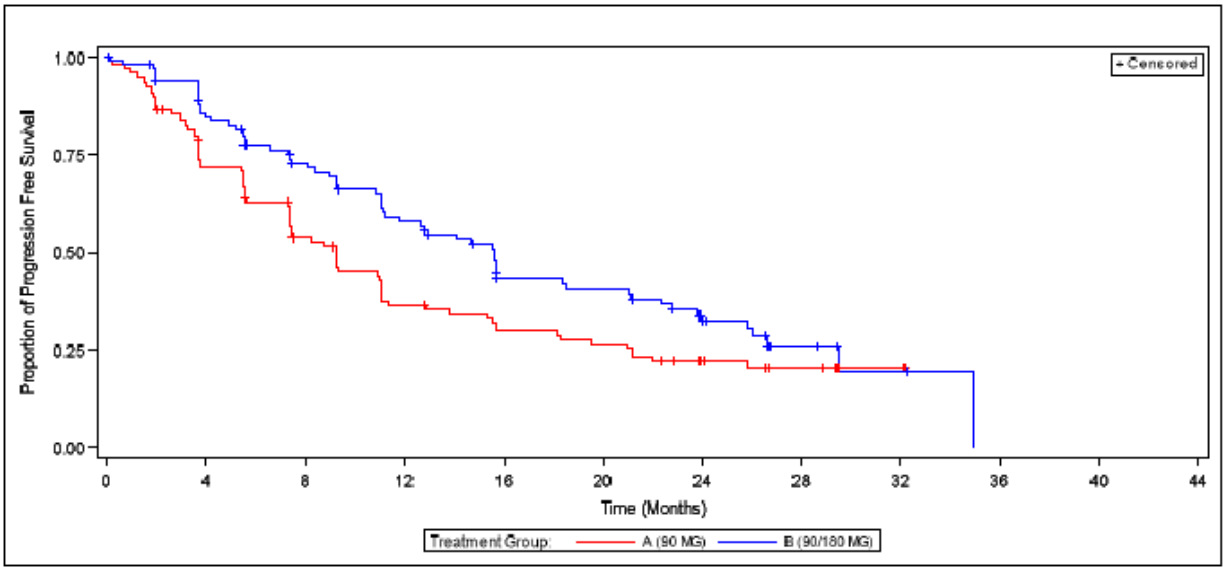
Table 36: IRC-Assessed Intracranial Objective Response in Patients with Measurable and only Nonmeasurable Brain Metastases at Baseline and by History of CNS Irradiation (cutoff: 28Feb2017)

	Patients with Measurable Brain Metastases			Patients with Only Nonmeasurable Brain Metastases		
Intracranial Efficacy Parameter	Arm A 90 mg QD N = 26	Arm B 90 mg QD →180 mg QD N = 18	Total N = 44	Arm A 90 mg QD N = 54	Arm B 90 mg QD →180 mg QD N = 55	Total N = 109
Overall, Confirmed Intracranial Objective Response Rate[a]						
n (%)	13/26 (50.0)	12/18 (66.7)	25/44 (56.8)	4/54 (7.4)	10/55 (18.2)	14/109 (12.8)
95% CI[b]	(29.9-70.1)	(41.0- 86.7)	(41.0- 71.7)	(2.1-17.9)	(9.1-30.9)	(7.2-20.6)
Prior CNS irradiation within 6 months of first dose, Confirmed Intracranial Objective Response Rate[a]						
n (%)	3/5 (60.0)	N/A	3/5 (60.0)	1/21 (4.8)	2/15 (13.3)	3/36 (8.3)
95% CI[b]	(14.7- 94.7)	N/A	(14.7-94.7)	(0.1-23.8)	(1.7-40.5)	(1.8-22.5)
Prior CNS irradiation ≥6 months after first dose, Confirmed Intracranial Objective Response Rate[a]						
n (%)	2/3 (66.7)	3/4 (75.0)	5/7 (71.4)	0/19	3/24 (12.5)	3/43 (7.0)
95% CI[b]	(9.4-99.2)	(19.4- 99.4)	(29.0- 96.3)	(0.0-15.8)	(2.7-32.4)	(1.5-19.1)
No prior CNS irradiation, Confirmed Intracranial Objective Response Rate[a]						
n (%)	8/18 (44.4)	9/14 (64.3)	17/32 (53.1)	3/14 (21.4)	5/16 (31.3)	8/30 (26.7)
95% CI[b]	(21.5-69.2)	(35.1-87.2)	(34.7-70.9)	(4.7-50.8)	(11.0- 58.7)	(12.3- 45.9)

Source: Study AP26113-13-201 Tables 14.2.20.9 and 14.2.20.10 (Data Extraction Date: 21 February 2017; last scan date 28 February 2017, respectively).
Abbreviations: CI = confidence interval; CNS = central nervous system; IRC = Independent Review Committee; n = number; NA = not applicable.
a Confirmed intracranial objective response rate is defined as the proportion of patients who are confirmed to have achieved CR or PR per RECIST v1.1 after study drug initiation.
b The 95% confidence intervals were calculated using the exact binomial method.

Progression-free survival

The KM estimate median investigator-assessed PFS was 9.2 months (95% CI: 7.4, 11.0) for the 90 mg group (77 events [68.8%]) and 15.6 months (95% CI: 11.1, 21) for the 90 mg/180 mg group (64 events [58.2%]). In a post-hoc analysis, the hazard ratio (HR) for PFS observed between the two arms was 0.68 (95% CI: 0.49, 0.95).



Source: Figure 14.2.1.7.
Abbreviations: ITT, intent to treat; PFS, progression-free survival.
In this analysis, PFS was defined as the time from initiation of treatment until the date at which disease progression was first evident or death, whichever comes first.

Figure 18: Investigator-Assessed Systemic PFS (ITT Population: by Treatment Group)

The KM estimate median IRC-assessed PFS was 9.2 months (95% CI: 7.4, 12.8) for the 90 mg group (65 events [58.0%]) and 16.7 months (95% CI: 11.6, 21.4) for the 90/180 mg group (54 events [49.1%]). In a post-hoc analysis, the HR for IRC-assessed PFS between the two arms was 0.75 (95% CI: 0.37, 1.08).

In sensitivity analysis of investigator-assessed PFS (cut-off 31 May2016), all patients with an observed progression or death (regardless of timing) are classified as events. The KM estimate median PFS was 8.2 months (95% CI: 6.7, 11.0) for the 90 mg group and 12.9 months (95% CI: 10.8, 18.4) for the 90/180 mg group.

Table 37: Progression-Free Survival by Best Response in Study (cutoff 31May2016)

	Median IRC-Assessed PFS (months, 95%CI)	
	Arm A	Arm B
IRC-Assessed Best Response	Brigatinib 90 mg QD	Brigatinib 90 mg QD → 180 mg QD
CR/PR (Arm A: N=57; Arm B: N=60)	18.2 (10.8, NR)	17.9 (15.6, NR)
SD (Arm A: N=30; Arm B: N=32)	5.5 (3.6, 11.1)	9.3 (3.7, NR)
PD (Arm A: N=14; Arm B: N=5)	1.8 (1.4, 1.9)	1.8 (1.7, 1.8)

Overall Survival

The KM median overall survival (OS) is 29.5 months in the 90 mg group (95% CI, 18.2-not reached [NR]) and is 34.1 months (95% CI, 27.7-NR) in the 90/180 mg group, with 50 of 112 (44.6%) and 40 of 110 (36.4%) events observed in the 90 mg group and the 90/180 mg group, respectively. The HR observed between the 2 arms is 0.70 (95% CI, 0.46-1.07),

The 12- and 24-month probabilities of survival were 70.3% and 54.6%, respectively, for patients in the 90 mg group and 80.1% and 66.1%, respectively, for patients in the 90/180 mg group.

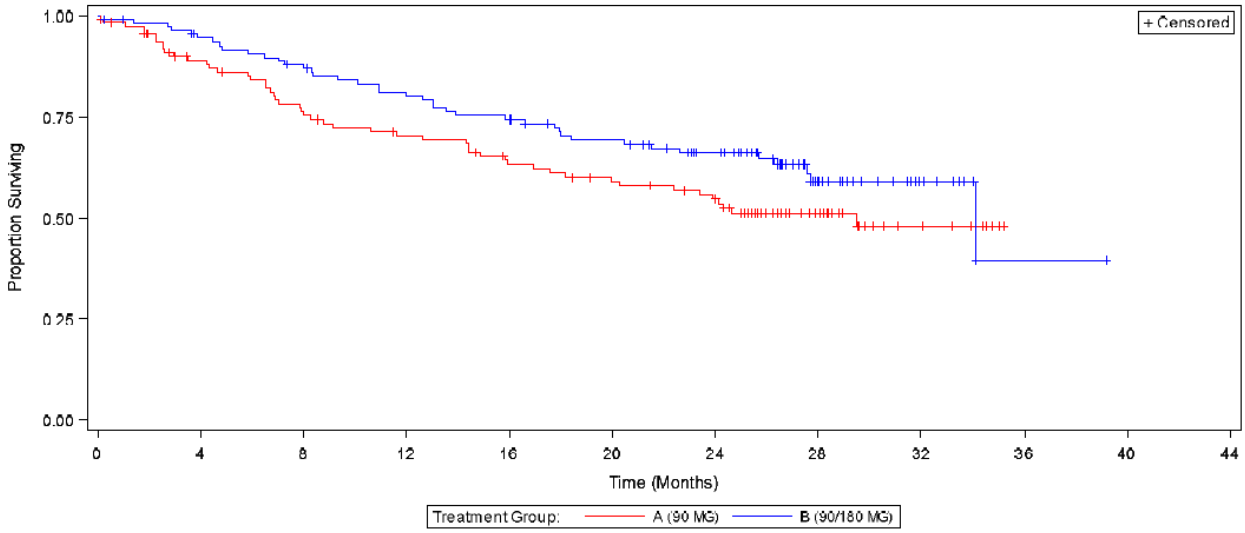


Figure 19: Kaplan-Meier Plot of Overall Survival: ITT Population by Treatment Arm

Disease Control Rate ()

Patient-Reported Quality of Life Assessment (EORTC QLQ-C30)

At baseline the mean (SD) transformed Global Health Status/QOL score, for 216/222 patients in the ITT population was 55.44 (25.61), with mean (SD) scores of 52.39 (27.42) for Arm A and 58.49 (23.40) for Arm B. There was no evidence that Global Health Status/QOL Scale scores differed between Arm A and Arm B (p=0.8578).

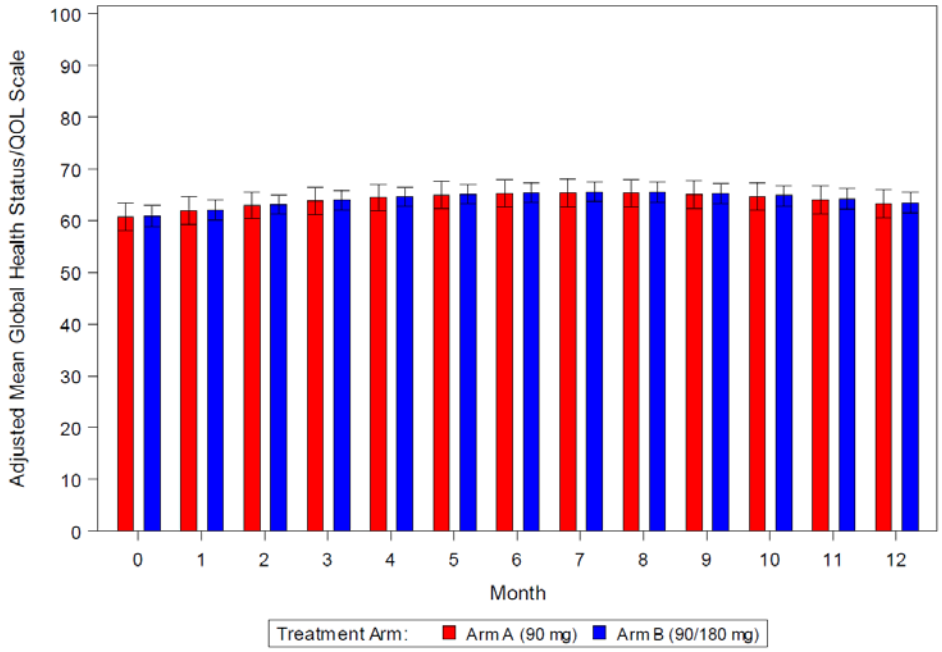


Figure 20: Adjusted Mean Scores for Transformed Global Health Status/QOL Scale over Time (ITT Population)

Ancillary analyses

Imbalances in baseline characteristics

The baseline differences that are expected to affect prognosis (age and ECOG performance score) are not balanced between the treatment groups. The Applicant has provided an analysis on the effect on the hazard ratio of adjusting for these factors, see below.

Table 38: Time to Event Endpoint Hazard Ratios, Unadjusted vs Adjusted for ECOG and Age in Study AP26113-13-201

	Hazard Ratio	
Endpoint	**(Arm B vs. Arm A), Unadjusted**	**(Arm B vs. Arm A), Adjusted**
Investigator-assessed PFS (95% CI)	0.64 (0.45-0.91)	0.64 (0.45-0.92)
IRC-assessed PFS (95% CI)	0.69 (0.47-1.02)	0.66 (0.44-0.98)
Overall Survival (95% CI)	0.67 (0.42-1.06)	0.63 (0.39-1.01)

CI = confidence interval; IRC = institutional review committee; OS = overall survival; PFS = progression-free survival;
Source: AP26113-13-201 Tables 14.2.3.7, 14.2.1.6, 14.2.20.6, 14.2.20.7 and 14.2.20.8 (Data extraction date: 21 February 2017).

The results across endpoints are generally consistent between the unadjusted and adjusted analyses, with the adjusted analyses showing similar or lower hazard ratios compared with the unadjusted analyses.

Responses by smoking status

Table 39: Investigator-Assessed Objective Response Rate by Baseline Smoking Status (ITT Population)

		Investigator-Assessed ORR		
Efficacy Parameter		Arm A 90 mg QD	Arm B 90 mg QD → 180 mg QD	Total
Overall ITT, Confirmed Objective Response Rate[a]	n/N (%)	51/112 (45.5)	61/110 (55.5)	112/222 (50.5)
	95% CI[b]	(36.1-55.2)	(45.7-64.9)	(43.7-57.2)
Never Smoked, Confirmed Objective Response Rate[a]	n/N (%)	36/71 (50.7)	41/63 (65.1)	77/134 (57.5)
	95% CI[b]	(38.6-62.8)	(52.0-76.7)	(48.6-66.0)
Former Smoker, Confirmed Objective Response Rate[a]	n/N (%)	14/34 (41.2)	20/43 (46.5)	34/77 (44.2)
	95% CI[b]	(24.6-59.3)	(31.2-62.3)	(32.8-55.9)
Current Smoker, Confirmed Objective Response Rate[a]	n/N (%)	0/6	0/4	0/10
	95% CI[b]	(0.0-50.0)	(0.0-75.0)	(0.0-30.0)
Unknown Smoking History, Confirmed Objective Response Rate[a]	n/N (%)	1/1 (100.0)	N/A	1/1 (100.0)
	95% CI[b]	(2.5-100.0)	N/A	(2.5-100.0)

Responses by ALK mutation status

Tumour tissue samples collected after progression on crizotinib but prior to initiation of brigatinib treatment (baseline), or samples collected after disease progression on brigatinib therapy (post-baseline) were analyzed by DNA sequencing using the FoundationOne Next Generation Sequencing (NGS) platform. Baseline samples were evaluable in 17 patients. ALK rearrangements were detected in 13/17 patients centrally by NGS and secondary mutations in the ALK kinase domain (KD) were detected in 4/17 patients; secondary mutations were only observed in patients with a NGS-detectable ALK rearrangement. Confirmed responses were observed in patients with ALK rearrangements by NGS

in the 90 mg and 90/180 mg group (PR in 3/6 and 6/7 patients, respectively), including a confirmed PR in a patient with the G1202R mutation at baseline. Of the 13 patients with NGS-detected ALK rearrangements, confirmed responses were observed in 6 of the 9 patients without secondary ALK KD mutations (6 PR), and 3/4 patients with secondary mutations (3 PR). Of the 4 patients in whom no ALK rearrangement was detected by NGS at baseline, 1 had a confirmed response (PR). A post-baseline tumour tissue sample was evaluable in one patient (90 mg QD). Two secondary ALK KD mutations were detected in this sample - F1174L and E1210K (both mutations in the same ALK allele). This patient had a confirmed response with a time to progression of 225 days. No baseline tissue for this patient was available for analysis.

Table 40: Responses to brigatinib in patients with tumour or plasma samples at baseline according to ALK mutation status

	Tumour	Plasma	Total[a]
Patients with baseline data, n	32	67	91
Confirmed ORR, n/N (%)	22/32 (69%)	33/67 (49%)	53/91 (58%)
Patients with detectable ALK fusion, n	27	30	54
Confirmed ORR, n/N (%)	21/27 (78%)	17/30 (57%)	35/54 (65%)
Patients with secondary ALK mutations, n	9	10	19
Confirmed ORR, n/N (%)	7/9 (78%)	5/10 (50%)	12/19 (63%)
Patients without secondary ALK mutations, n	18	20	35
Confirmed ORR, n/N (%)	14/18 (78%)	12/20 (60%)	23/35 (66%)

[a] 8 patients had both tumour and plasma samples analyzed (6/8 confirmed ORR); 3 of these patients had an ALK fusion detected in both samples (3/3 confirmed ORR); in two of these patients no ALK secondary mutation was detected in either tumor or plasma; in one of these patients an ALK secondary mutation was detected in tumor but not plasma – for the purpose of combining the 2 datasets this patient was considered to have an ALK secondary mutation.

Results from a matching-adjusted indirect comparisons (MAIC) analysis of the efficacy of brigatinib compared with alectinib and ceritinib.

In order to further support the assessment, the applicant conducted a MAIC in order to estimate relative treatment effect versus ceritinib and alectinib.

Table 41: Trial Designs

	Study 201 Brigatinib (Arm B)	ASCEND-1 Ceritinib	ASCEND-2 Ceritinib	NP28673 Alectinib	NP28761 Alectinib
No. of patients	110	163	140	138	87
Center	Multi-center	Multi-center	Multi-center	Multi-center	Multi-center
Geography	North America (US and Canada), EU, Asia and Australia	North America (US and Canada), EU, Asia and Australia	North America (US and Canada), EU, and Asia	US, EU, Asia and Australia	North America (US and Canada)
Phase	2	1	2	2	2
Design	Patients randomized to 2 dosing regimen arms	Single-arm study	Single-arm study	Single-arm study	Single-arm study
Blinding	Open-label	Open-label	Open-label	Open-label	Open-label
Dose	180 mg QD with 7-day lead-in at 90 mg QD (Arm B)	750 mg QD	750 mg QD	600 mg BID	600 mg BID
Median follow-up	17.9 months	11.1 months	11.3 months	21.0 months	17.0 months
Interval between scans	8 weeks	8 weeks	8 weeks	8 weeks	8 weeks
Disease Assessment Criteria	RECIST 1.1	RECIST 1.0	RECIST 1.1	RECIST 1.1	RECIST 1.1
Primary Efficacy Endpoint	Investigator-assessed ORR	Investigator-assessed ORR	IRC-assessed ORR	IRC-assessed ORR	IRC-assessed ORR

Sources: AP26113-13-201 Protocol Amendment 2, ASCEND-1 (Kim DW, 2017), ASCEND-2 (Mok T, 2015), NP28673 (Barlesi F, 2016), NP28761 (Camidge DR, 2017)

Table 42: Key Inclusion and Exclusion Criteria

	ALTA Brigatinib	ASCEND-1 Ceritinib	ASCEND-2 Ceritinib	NP28673 Alectinib	NP28761 Alectinib
INCLUSION CRITERIA					
Age category	≥18	≥18	≥18	≥18	≥18
Documented ALK rearrangement	X	x	x	x	x
ECOG performance status	0 – 2	0 – 2	0 – 2	0 – 2	0 – 2
PRIOR TREATMENT					
Treated with crizotinib	X	x (subgroup)	x	x	x
Progressed on crizotinib	X		x	x	x
Treatment with chemotherapy	Allowed naïve and chemo-treated	Allowed naïve and chemo-treated	Chemo-treated	Allowed naïve and chemo-treated	Allowed naïve and chemo-treated
EXCLUSION CRITERIA					
Prior treatment with ALK inhibitor (excluding crizotinib)	X		x	x	x

Sources: AP26113-13-201 Protocol Amendment 2, (Ou SH, 2016) (PROFILE 1001/1005), ASCEND-1 (Kim DW, 2017), ASCEND-2 (Mok T, 2015), NP28673 (Ou SH, 2016), NP28761 (Gandhi L Shaw AT, Gadgeel S, 2015)

Comparison of trial designs

Comparison of brigatinib with ceritinib

Table 43: Comparison of Pre-Match and Post-Match Baseline Characteristics in Study 201 Arm B with ASCEND-1

Factor	ASCEND-1	Study 201 Arm B (Pre-Match)	Study 201 Arm B (Post-Match)
Age (median, years)	52	56.5	51
Sex – Male (%)	46	42	46
Race – Asian (%)	29	27	29
ECOG PS 0 (%)	23	41	23
ECOG PS 1 (%)	64	51	64
ECOG PS 2 (%)	13	8	13
Previous chemotherapy – Yes (%)	84	74	84
Smoker – Current (%)	3	4	3
Brain Metastases (%)	60	67	60

Table 44: Comparison of Pre-Match and Post-Match Baseline Characteristics in Study 201 Arm B with ASCEND-2

Factor	ASCEND-2	Study 201 Arm B (Pre-Match)	Study 201 Arm B (Post-Match)
Age (median, years)	51	56.5	50
Sex – Male (%)	50	42	50
Race – Asian (%)	38	27	38
Race – White (%)	60	69	60
ECOG PS 0 (%)	30	41	30
ECOG PS 1 (%)	56	51	56
ECOG PS 2 (%)	14	8	14
Previous chemotherapy – Yes (%)	100	74	100
Brain Metastases (%)	71	67	71
Last treatment was crizotinib (%)	100	96	100

Table 45: Indirect Comparison of Efficacy Outcomes Between Brigatinib and Ceritinib in ASCEND-1 Before and After Matching

Outcome	ASCEND-1	Study 201 Arm B (Before Matching)	Study 201 Arm B (After Matching)
ORR (95% CI)	56% (49%, 64%)	55% (46%, 65%)	53% (42%, 65%)

Outcome	ASCEND-1	Study 201 Arm B (Before Matching)	Study 201 Arm B (After Matching)
Odds Ratio (95% CI)	Reference	0.96 (0.59, 1.57)	0.88 (0.51, 1.53)
Median DOR, months (95% CI)	7.7 (6.3, 9.5)	13.8 (10.8, 19.3)	13.8 (10.2, 19.3)
DOR Hazard Ratio (95% CI)	Reference	0.45 (0.29, 0.69)	0.44 (0.27, 0.73)
Median PFS, months (95% CI)	6.6 (5.8, 9.0)	15.6 (11.2, 21.0)	15.7 (11.8, 21.1)
PFS Hazard Ratio (95% CI)	Reference	0.40 (0.29, 0.56)	0.38 (0.26, 0.57)

Note: Investigator-assessed data from both studies were used for ORR, DOR and PFS analyses here. OS Kaplan-Meier curves were not available for ASCEND-1 and so a comparison of OS was not possible in this analysis.

Table 46: Indirect Comparison of Efficacy Outcomes Between Brigatinib and Ceritinib in ASCEND-2 Before and After Matching

Outcome	ASCEND-2	Study 201 Arm B (Before Matching)	Study 201 Arm B (After Matching)
ORR (95% CI)	36% (28%, 44%)	55% (45%, 64%)	55% (41%, 68%)
Odds Ratio (95% CI)	Reference	2.16 (1.30, 3.61)	2.17 (1.13, 4.20)
Median DOR, months (95% CI)	11.1 (9.6, NR)	14.8 (13.6, NR)	NR (14.8, NR)
DOR Hazard Ratio (95% CI)	Reference	0.45 (0.26, 0.81)	0.28 (0.13, 0.61)
Median PFS, months (95% CI)	7.4 (6.1, 9.3)	16.7 (12.6, NR)	18.3 (11.6, NR)
PFS Hazard Ratio (95% CI)	Reference	0.40 (0.27, 0.58)	0.33 (0.20, 0.56)
12-month OS (95% CI)	64.8% (57.1, 73.5)	80.1% (72.9, 88.1)	83.0% (73.2, 94.1)
Median OS, months (95% CI)	14.8 (13.5, NR)	27.6 (27.6, NR)	27.6 (27.6, NR)
OS Hazard Ratio (95% CI)	Reference	0.44 (0.28, 0.69)	0.33 (0.17, 0.63)

Note: IRC-assessed data from both studies were used for ORR, DOR and PFS analyses here.

Comparison of brigatinib with alectinib

Table 47: Comparison of Pre-Match and Post-Match Baseline Characteristics in Study 201 Arm B With NP28673

Factor	NP28673	Study 201 Arm B (Pre-Match)	Study 201 Arm B (Post-Match)
Age (median, years)	52	56.5	51
Sex – Male (%)	44	42	44
Race – Asian (%)	26	27	26
Race – White (%)	67	69	67
ECOG PS 0 (%)	32	41	32
ECOG PS 1 (%)	59	51	59
ECOG PS 2 (%)	9	8	9
Previous chemotherapy – Yes (%)	80	74	80
Smoker – Never (%)	70	57	70
Best prior response – CR/PR (%)	54	66	54
Brain Metastases (%)	61	67	61

Table 48: Comparison of Pre-Match and Post-Match Baseline Characteristics in Study 201 Arm B With NP28761

Factor	NP28761	Study 201 Arm B (Pre-Match)	Study 201 Arm B (Post-Match)
Age (median, years)	54	56.5	53
Sex – Male (%)	45	42	45
Race – Asian (%)	8	27	8
Race – White (%)	84	69	84
ECOG PS 0 (%)	35	41	35
ECOG PS 1 (%)	55	51	55
ECOG PS 2 (%)	10	8	10
Previous chemotherapy – Yes (%)	74	74	74
Smoker – Never (%)	62	57	62
Smoker – Former (%)	38	39	38
Brain Metastases (%)	60	67	60

Table 49: Indirect Comparison of Efficacy Outcomes Between Brigatinib and Alectinib in NP28673 Before and After Matching

Outcome	NP28673	Study 201 Arm B (Before Matching)	Study 201 Arm B (After Matching)
ORR (95% CI)	51% (42%, 60%)	55% (45%, 64%)	54% (42%, 66%)
Odds Ratio (95% CI)	Reference	1.16 (0.69, 1.95)	1.14 (0.63, 2.06)
Median DOR, months (95% CI)	16.4 (12.6, NR)	14.8 (13.6, NR)	15.6 (13.8, NR)
DOR Hazard Ratio (95% CI)	Reference	1.10 (0.66, 1.84)	0.95 (0.52, 1.73)
Median PFS, months (95% CI)	9.4 (6.5, 14.5)	16.7 (12.6, NR)	17.6 (12.6, NR)
PFS Hazard Ratio (95% CI)	Reference	0.64 (0.45, 0.92)	0.61 (0.40, 0.93)
12-month OS (95% CI)	74.7% (67.7, 82.4)	80.1% (72.9, 88.1)	79.5% (70.4, 89.7)
Median OS, months (95% CI)	25.9 (21.5, NR)	27.6 (27.6, NR)	27.6 (27.6, NR)
OS Hazard Ratio (95% CI)	Reference	0.69 (0.45, 1.06)	0.66 (0.39, 1.09)

Note: IRC-assessed data from both studies were used for ORR, DOR and PFS analyses here.

Table 50: Indirect Comparison of Efficacy Outcomes Between Brigatinib and Alectinib in NP28761 Before and After Matching

Outcome	NP28761	Study 201 Arm B (Before Matching)	Study 201 Arm B (After Matching)
ORR (95% CI)	52% (40%, 65%)	55% (45%, 64%)	53% (42%, 64%)
Odds Ratio (95% CI)	Reference	1.10 (0.60, 2.02)	1.04 (0.54, 2.00)
Median PFS, months (95% CI)	8.4 (6.4, 13.6)	16.7 (12.6, NR)	17.6 (11.6, NR)
PFS Hazard Ratio (95% CI)	Reference	0.59 (0.40, 0.87)	0.56 (0.36, 0.86)
12-month OS (95% CI)	70.0% (60.7, 80.6)	80.1% (72.9, 88.1)	75.3% (66.2, 85.7)
Median OS, months (95% CI)	23.0 (17.4, NR)	27.6 (27.6, NR)	27.6 (27.6, NR)
OS Hazard Ratio (95% CI)	Reference	0.60 (0.37, 0.97)	0.70 (0.42, 1.16)

Table 51: Comparison of Median PFS Between Alectinib in ALUR and Ceritinib in ASCEND-5 in a Post- Crizotinib Population

Study	Treatment	Median PFS, mo (95% CI)
ASCEND-5	Ceritinib	5.4 (4.1, 6.9) [IRC-assessed]
	Chemotherapy	1.6 (1.4, 2.8) [IRC-assessed]
ALUR	Alectinib	9.6 (6.9, 12.2) [investigator-assessed]
	Chemotherapy	1.4 (1.3, 1.6) [investigator-assessed]
	Alectinib	7.1 (6.3, 10.8) [IRC-assessed]
	Chemotherapy	1.6 (1.3, 4.1) [IRC-assessed]

Source: (Scagliotti G, 2016); (Novello S, 2017)

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 52: Summary of Efficacy for trial AP26113-13-201

Title: Main efficacy results for Study AP26113-13-201			
Study identifier	Study AP26113-13-201		
Design	A phase 2, open-label, randomized, multicentre, study in patients with advanced ALK+ NSCLC previously treated with crizotinib		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Follow-up (for survival and subsequent anti-cancer therapy) for 2 years after last patient enrolled in study. N/A N/A
Hypothesis	Exploratory		
Treatments groups	90 mg		90 mg brigatinib once daily
	90/180 mg		90 mg daily for 7 days, then increase to 180 mg daily
Endpoints and definitions	Primary endpoint	ORR by INV	Confirmed ORR (proportion of patients with confirmed CR or PR), as assessed by the investigator, per RECIST v1.1 after initiation of study drug in the ITT population
	Secondary endpoint	ORR by IRC	Confirmed ORR, as assessed by IRC, per RECIST v1.1 after initiation of study drug in the ITT population
	Secondary endpoint	Disease control rate	Proportion of patients who were confirmed to have achieved CR or PR or have a best overall response as SD for 6 weeks or more
	Secondary endpoint	Time to response	Time interval from the date of the first dose of study drug until the initial observation of CR or PR for patients with confirmed CR/PR
	Secondary endpoint	Duration of response	Time interval from the time that the measurement criteria were first met for CR/PR (whichever is first recorded) until the first date that the progressive disease was objectively documented or death
	Secondary endpoint	PFS	Time interval from the date of the first dose of study drug until the first date at which disease progression was objectively documented, or death due to any cause, whichever occurred first, in the ITT population
	Secondary endpoint	OS	Time interval from the date of the first dose of study drug until death due to any cause in the ITT population
	Secondary endpoint	Intracranial ORR	Confirmed intracranial ORR by IRC, per modification of RECIST v1.1 (in patients who have active brain metastases at baseline) – for patients with non-measurable lesions this was a CR.
	Secondary endpoint	Intracranial PFS	Confirmed intracranial PFS by IRC, per modification of RECIST v1.1 (in patients who have active brain metastases at baseline)
Database lock	29/09/2017		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Intent to treat when all patients had completed Cycle 5 disease assessment		
Descriptive statistics and estimate variability	Treatment group	90 mg	90/180 mg
	Number of subject (ITT)	112	110

	ORR by INV (%) 97.5% CI	45.5 34.8, 56.5	56.4 45.2, 67.0
	ORR by IRC (%) 95% CI	50.9 41.3, 60.5	56.4 46.6, 65.8
	Median time to response by INV (months) Range	1.8 1.7 – 7.3	1.9 1.0-11.0
	KM estimate median duration of response by INV (months) 95% CI	12.0 9.2, 17.7	13.8 10.2, 19.3
	KM estimate median PFS (months) by INV 95% CI	9.2 7.4, 11.1	15.6 11.1, 21.0
	KM estimate median PFS (months) by IRC 95% CI	9.2 7.4, 12.8	16.7 11.6, 21.4
	KM estimate median OS (months) 95% CI	29.5 18.2, NR	34.1 27.7, NR
	Intracranial ORR by IRC (%) 95% CI	50.0 29.9, 70.1	66.7 41.0, 86.7
	Intracranial PFS by IRC (months) 95% CI	11.1 5.6, 23.7	18.5 4.9, NR
Effect estimate per comparison	Secondary: OS	Comparison groups	90/180 mg vs 90 mg
		Hazard ratio	0.70
		95% CI	0.46, 1.07
	Secondary: PFS by INV	Comparison groups	90/180 mg vs 90 mg
		Hazard ratio	0.68
		95% CI	0.49, 0.95
	Secondary: PFS by IRC	Comparison groups	90/180 mg vs 90 mg
		Hazard ratio	0.75
		95% CI	0.37, 1.08

INV = investigator-assessed; ORR = objective response rate; IRC = independent review committee; CR = complete response; PR = partial response; SD = stable disease; PFS = progression-free survival; OS = overall survival; CI = confidence interval; NR = not reached

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

Table 53: **Clinical Studies in Special Populations (Studies AP26113-13-101 and AP26113-13-201)**

	Age <65 years	Age 65-74 years	Age 75-84 years	Age 85 + years
Controlled Trials, n/N (%)	0	0	0	0
Non-Controlled Trials, n/N (%)	268/359 (74.7)	74/359 (20.6)	17/359 (4.7)	0

Source: Table 14.1.1.4 (Data Extraction Date: 21 February 2017).

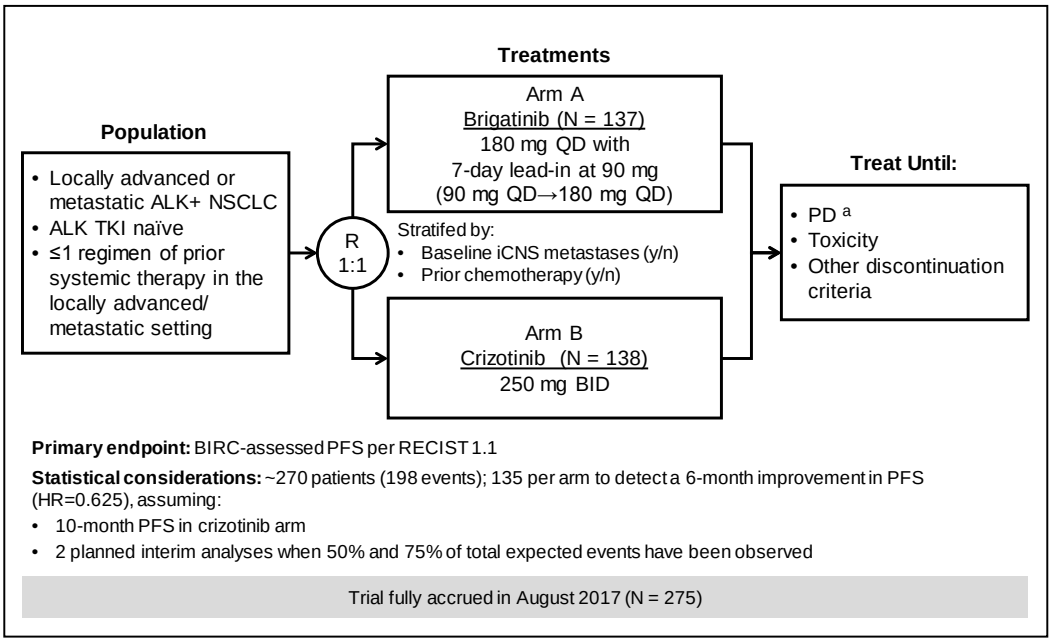
Supportive studies

Study 101 provides supportive evidence of efficacy for the proposed dose in the target population (see above).

In addition, top-line results from the ongoing phase 3 trial (AP-26113-13-301) were submitted.

Top-line results from AP-26113-13-301

This study was a phase 3, randomised, open-label, comparative, multicentre, international study in patients with advanced ALK+ NSCLC who had not previously received an ALK inhibitor, or any other TKI, or more than one regimen of prior systemic therapy in the advanced setting. Patients were required to have at least one measurable lesion per RECIST version 1.1. ALK testing could be conducted locally for eligibility, but confirmed centrally retrospectively. Patients with symptomatic CNS metastases were excluded. Patients were randomized in a 1:1 fashion to receive either brigatinib at the proposed dose (90 mg → 180 mg QD) or crizotinib (250 mg BID).



Abbreviations: ALK+, anaplastic lymphoma kinase positive; BID, twice daily; BIRC, blinded independent review committee; HR, hazard ratio; iCNS, intracranial central nervous system; MRI, magnetic resonance imaging; NSCLC, non–small-cell lung cancer; PD, progressive disease; PFS, progression-free survival; QD, once daily; R, randomization; RECIST; Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor; y/n, yes/no.
Disease assessments (including brain MRI for all patients) occurred every 8 weeks.
[a] Crossover to brigatinib was allowed for patients randomized to crizotinib (Arm B) after documentation of BIRC-assessed progression.

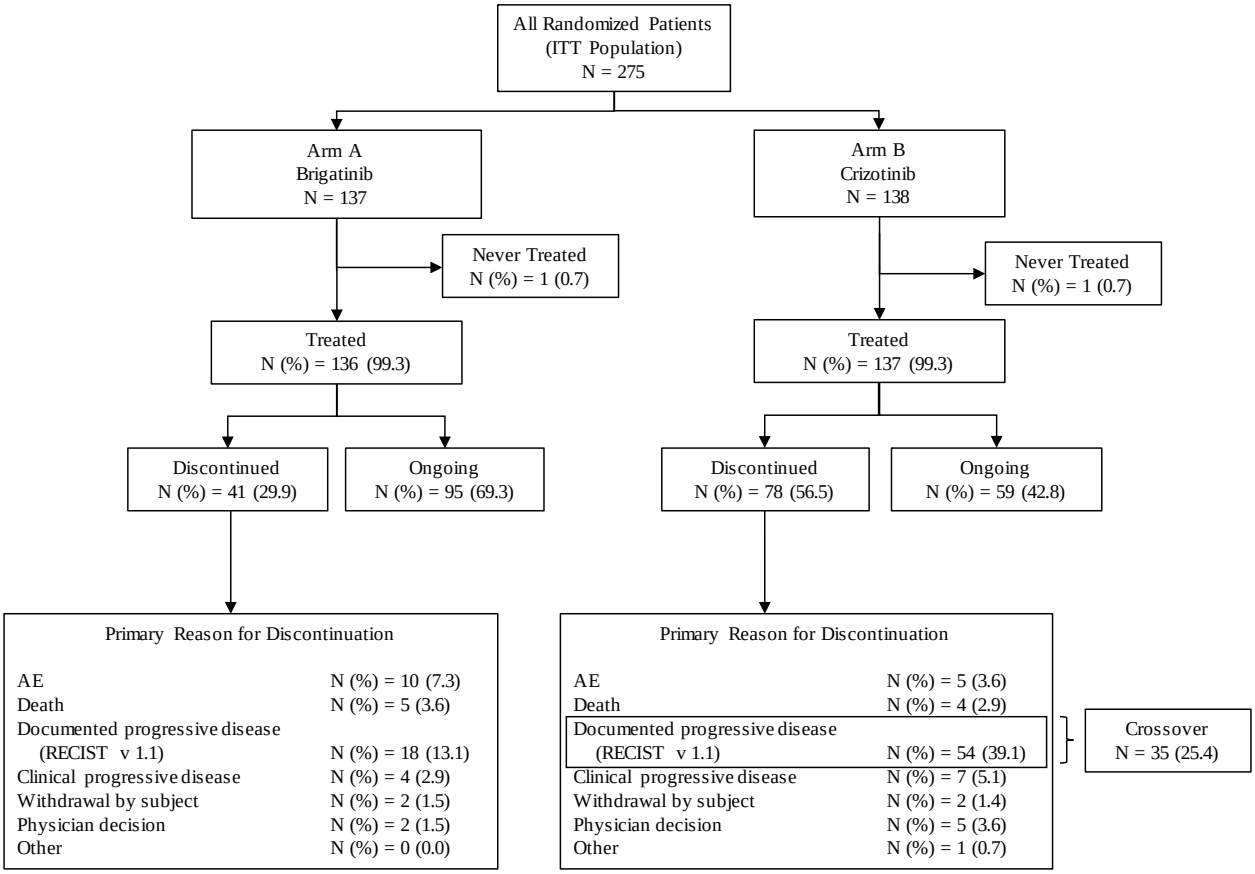
Figure 21: Study 301: Phase 3, Randomized Study in TKI-Naïve ALK+ NSCLC

Efficacy Endpoints

The primary endpoint was BIRC-assessed PFS per RECIST v1.1. Key secondary endpoints were confirmed ORR, confirmed intracranial ORR, intracranial PFS and OS. Global health status/quality of life (EORTC QLQ C30) and time to deterioration of dyspnoea (EORTC QLQ-LC13) were also evaluated. The primary endpoint, PFS by blinded independent review (BIRC) is endorsed, as the study was not blinded and PFS is considered a clinically relevant endpoint in the first-line palliative treatment setting in a randomized trial. The other secondary endpoints are also appropriate.

Patients

The median duration of follow-up is considered short, with 11 and 9.3 months follow-up in each arm. The demographic and baseline characteristics reflect the target population: the majority were female, never smokers, had stage IV disease and had not received prior chemotherapy for advanced disease. Median age was 58 years. Around 30% had intracranial CNS metastases at baseline.



Source: Study 301 Table 15.1.3 (data cutoff: 19 February 2018).

Abbreviations: AE, adverse event; ITT, intent-to-treat; RECIST, Response Evaluation Criteria in Solid Tumours.

Figure 22: Disposition of Patients

Table 54: Demographics (ITT Population)

	Arm A Brigatinib (N = 137)	Arm B Crizotinib (N = 138)	Total (N = 275)
Age, years			
Mean (SD)	57.9 (13.47)	58.6 (11.42)	58.2 (12.47)
Median	58.0	60.0	59.0
Minimum, Maximum	27, 86	29, 89	27, 89
Age categories (years), N (%)			
18-64	93 (67.9)	95 (68.8)	188 (68.4)
≥65	44 (32.1)	43 (31.2)	87 (31.6)
18-49	40 (29.2)	30 (21.7)	70 (25.5)
50-64	53 (38.7)	65 (47.1)	118 (42.9)
65-74	26 (19.0)	31 (22.5)	57 (20.7)
≥75	18 (13.1)	12 (8.7)	30 (10.9)
Gender, N (%)			
Female	69 (50.4)	81 (58.7)	150 (54.5)
Male	68 (49.6)	57 (41.3)	125 (45.5)
Race, N (%)			
Asian	59 (43.1)	49 (35.5)	108 (39.3)
Black or African American	0	2 (1.4)	2 (0.7)
White	76 (55.5)	86 (62.3)	162 (58.9)
Unknown	2 (1.5)	1 (0.7)	3 (1.1)
Ethnicity, N (%)			
Hispanic, Latino, or Spanish	6 (4.4)	10 (7.2)	16 (5.8)
Geographical region, N (%)			
Asia Pacific	58 (42.3)	49 (35.5)	107 (38.9)
Europe	69 (50.4)	74 (53.6)	143 (52.0)
North America	10 (7.3)	15 (10.9)	25 (9.1)

Source: Study 301 Table 15.1.6.1 (data cutoff: 19 February 2018).
Abbreviations: ITT, intent-to-treat.

Table 55: Baseline Characteristics (ITT Population)

	Arm A Brigatinib (N = 137)	Arm B Crizotinib (N = 138)	Total (N = 275)
Cigarette smoking history, N (%)			
Never	84 (61.3)	75 (54.3)	159 (57.8)
Current	4 (2.9)	7 (5.1)	11 (4.0)
Former	49 (35.8)	56 (40.6)	105 (38.2)
ECOG performance status, N (%)			
0	58 (42.3)	60 (43.5)	118 (42.9)
1	73 (53.3)	72 (52.2)	145 (52.7)
2	6 (4.4)	6 (4.3)	12 (4.4)
Diagnosis stage at study entry, N (%)			
IIIB	8 (5.8)	12 (8.7)	20 (7.3)
IV	129 (94.2)	126 (91.3)	255 (92.7)
Time since initial diagnosis, months			
Mean (SD)	10.23 (23.211)	12.51 (27.948)	11.38 (25.676)
Median	1.68	1.48	1.61
Minimum, Maximum	0.1, 145.3	0.3, 189.8	0.1, 189.8
Histopathological classification, N (%)			
Adenocarcinoma	126 (92.0)	137 (99.3)	263 (95.6)
Adenosquamous carcinoma	3 (2.2)	1 (0.7)	4 (1.5)
Large-cell	2 (1.5)	0	2 (0.7)
Squamous	4 (2.9)	0	4 (1.5)
Other	2 (1.5)	0	2 (0.7)
Organ involvement at study entry, N (%) [a]			
Lung	126 (91.9)	127 (92.1)	253 (92.0)
Other organ	134 (97.8)	133 (96.4)	267 (97.1)
Liver	31 (22.6)	24 (17.4)	55 (20.0)
Bone	35 (25.5)	50 (36.2)	85 (30.9)
Brain - Leptomeningeal	4 (2.9)	3 (2.2)	7 (2.5)
Brain - Parenchymal	37 (27.0)	39 (28.3)	76 (27.6)
iCNS metastasis at baseline, N (%) [b, c]	40 (29.2)	41 (29.7)	81 (29.5)
Prior chemotherapy for locally advanced or metastatic disease, N (%) [c]	36 (26.3)	37 (26.8)	73 (26.5)

	Arm A Brigatinib (N = 137)	Arm B Crizotinib (N = 138)	Total (N = 275)

Source: Study 301 Table 15.1.6.2 (data cutoff: 19 February 2018).
Abbreviations: ECOG, Eastern Cooperative Oncology Group; iCNS, intracranial central nervous system; ITT, intent-to-treat.
[a] Patients may have more than 1 organ involved at study entry.
[b] As assessed by the investigator.
[c] Randomization stratification factor; proportion reflects actual number patients with this baseline characteristic, whether or not recorded at the time of randomization.

Efficacy Results

The planned IA shows results after 26.3% events in arm A and 45.7% events in arm B. The analysis met the predefined number of events (103) assessed by the investigator, and there were significantly more events in patients receiving crizotinib. The PFS HR of 0.492 (95% CI: 0.33, 0.74) between the arms is statistically significant.

Table 56: BIRC-Assessed PFS: First Interim Analysis of the Primary Endpoint (ITT Population)

	Arm A Brigatinib (N = 137)	Arm B Crizotinib (N = 138)
Number with events (%)	36 (26.3)	63 (45.7)
Death	6 (4.4)	6 (4.3)
PD	28 (20.4)	53 (38.4)
Palliative radiotherapy to the brain	2 (1.5)	4 (2.9)
Number censored (%)	101 (73.7)	75 (54.3)
PFS, months		
25th percentile (95% CI)	7.556 (5.52, NE)	3.975 (3.65, 5.55)
Median (95% CI)	NE (NE, NE)	9.758 (9.03, 12.88)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Minimum, maximum	0.03, 18.33	0.03, 18.33
KM estimate, % (95% CI) [N at risk]		
12 months	66.5 (56, 75) [N = 26]	42.6 (32, 53) [N = 18]
Log-rank p-value (brigatinib vs crizotinib)	0.0007	
HR (95% CI) (brigatinib vs crizotinib)	0.492 (0.33, 0.74)	
P-value	0.0008	

Source: Study 301 Table 15.2.1.1.1 (data cutoff: 19 February 2018).
Abbreviations: BIRC, blinded independent review committee; HR, hazard ratio; iCNS, intracranial central nervous system; ITT, intent-to-treat; KM, Kaplan-Meier; NE, not estimable; PD, progressive disease; PFS, progression-free survival.
P-values from a log-rank test stratified by presence of iCNS metastases and prior chemotherapy for locally advanced or metastatic disease at study entry. The HR and associated p-value were obtained using a Cox proportional hazards model with randomization stratification factors as covariates.

Confirmed ORR by BIRC was 70.8% for brigatinib vs 60.1% for crizotinib (p= 0.0678). Confirmed complete response was 3.6% for brigatinib vs 5.1% for crizotinib.

Table 57: BIRC-Assessed ORR (ITT Population)

	Arm A Brigatinib (N = 137)	Arm B Crizotinib (N = 138)
Best confirmed response, N (%)		
CR	5 (3.6)	7 (5.1)
PR	92 (67.2)	76 (55.1)
Stable disease	17 (12.4)	30 (21.7)
PD	7 (5.1)	9 (6.5)
NE [a]	16 (11.7)	16 (11.6)
Confirmed ORR [b]		
N (%)	97 (70.8)	83 (60.1)
(95% CI)	(62.43, 78.25)	(51.47, 68.38)
Odds ratio (95% CI) (brigatinib vs crizotinib) [c]	1.59 (0.96, 2.62)	
P-value [c]	0.0678	
ORR (confirmed + unconfirmed) [d]		
N (%)	104 (75.9)	101 (73.2)
(95% CI)	(67.87, 82.80)	(64.99, 80.37)
Odds ratio (95% CI) (brigatinib vs crizotinib) [c]	1.13 (0.66, 1.97)	
P-value [c]	0.6512	
iDCR [e]		
N (%)	117 (85.4)	119 (86.2)
(95% CI)	(78.36, 90.85)	(79.34, 91.50)
Odds ratio (95% CI) (brigatinib vs crizotinib) [c]	0.93 (0.47, 1.82)	

P-value [c]	0.8220

Source: Study 301 Table 15.2.2.1.1 and Table 15.2.2.2.1 (data cutoff: 19 February 2018).
Abbreviations: BIRC, blinded independent review committee; CR, complete response; iCNS, intracranial central nervous system; iDCR, intracranial disease control rate; ITT, intent-to-treat; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.
[a] Includes patients who had nonmeasurable disease at baseline by BIRC, died early, or with unknown response.
[b] Confirmed ORR was defined as the proportion of subjects who achieved confirmed CR or PR per RECIST v1.1.
[c] Odds ratios and p-values were from a Cochran-Mantel-Haenszel test stratified by presence of iCNS metastases at baseline, and prior chemotherapy for locally advanced or metastatic disease.
[d] ORR was defined as the proportion of subjects who achieved confirmed/unconfirmed CR or PR per RECIST v1.1
[e] iDCR was defined as the proportion of randomized patients who have achieved confirmed CR, PR, or stable disease. The criteria for stable disease must have been met at least once after randomization at a minimum interval of 6 weeks after randomization.

Table 58: Time to Response and DOR by BIRC Assessment (ITT Population, Confirmed Responders)

	Arm A Brigatinib (N = 137)	**Arm B Crizotinib (N = 138)**
Number with confirmed response (%)	97 (70.8)	83 (60.1)
Number censored (%)	80 (82.5)	58 (69.9)
Time to response (in confirmed responders), months		
Median (95% CI)	1.840 (1.84, 1.87)	1.873 (1.84, 1.87)
Minimum, maximum	1.02, 7.36	0.79, 7.43
DOR (in confirmed responders), months	(N = 97)	(N = 83)
Median (95% CI)	NE (NE, NE)	11.072 (9.23, NE)
Minimum, maximum	1.84, 16.46	1.45, 16.59
Kaplan-Meier estimate, % (95% CI) [N at risk]	(N = 97)	(N = 83)
12 months	78.0 (67, 86) [N = 7]	48.0 (31, 63) [N = 4]

Source: Study 301 Table 15.2.6.1 (data cutoff: 19 February 2018).
Abbreviations: BIRC, blinded independent review committee; DOR, duration of response; ITT, intent-to-treat; NE, not estimable.

Table 59: OS (ITT Population)

	Arm A Brigatinib (N = 137)	**Arm B Crizotinib (N = 138)**
Number with event (death) (%)	17 (12.4)	17 (12.3)
Number censored (%)	120 (87.6)	121 (87.7)
Time to death, months		
25th percentile (95% CI)	NE (13.01, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Minimum, maximum	0.07, 18.43	0.03, 19.29
Kaplan-Meier estimate, % (95% CI) [N at risk]		
12 months	85.0 (76, 91) [N = 40]	85.7 (77, 91) [N = 41]
Log-rank p-value (brigatinib vs crizotinib)	0.9386	
HR (95% CI) (brigatinib vs crizotinib)	0.983 (0.50, 1.93)	
p-value (brigatinib vs crizotinib)	0.9611	

Source: Study 301 Table 15.2.5.1.1 (data cutoff: 19 February 2018).
Abbreviations: HR, hazard ratio; iCNS, intracranial central nervous system; ITT, intent-to-treat; NE, not estimable; OS, overall survival.
P-values from a log-rank test stratified by randomization stratification factors at study entry (presence of iCNS metastases at baseline and prior chemotherapy for locally advanced or metastatic disease). The HR and associated p-value were obtained using a Cox proportional hazards model with randomization stratification factors as covariates.

Intracranial efficacy are assessable for a limited number of patients with measurable CNS metastases, i.e. 18 and 21 patients in arm A and B, respectively. For these patients confirmed intracranial ORR was 14/18 (77.8%) and 6/21 (28.6%) for brigatinib and crizotinib, respectively. Median intracranial DOR was NE in the brigatinib arm and 9.2 months in the crizotinib arm.

Table 60: BIRC-Assessed iORR in Patients with iCNS Metastases at Baseline

Baseline iCNS Metastases:	Measurable		Nonmeasurable		Any	
	Arm A Brigatinib (N = 18)	Arm B Crizotinib (N = 21)	Arm A Brigatinib (N = 25)	Arm B Crizotinib (N = 26)	Arm A Brigatinib (N = 43)	Arm B Crizotinib (N = 47)
Best Confirmed Response, N (%)						
CR	2 (11.1)	0	14 (56.0)	2 (7.7)	16 (37.2)	2 (4.3)
PR	12 (66.7)	6 (28.6)	1 (4.0)	0	13 (30.2)	6 (12.8)
Stable disease	2 (11.1)	11 (52.4)	6 (24.0)	17 (65.4)	8 (18.6)	28 (59.6)
PD	1 (5.6)	2 (9.5)	2 (8.0)	5 (19.2)	3 (7.0)	7 (14.9)
NE [a]	1 (5.6)	2 (9.5)	2 (8.0)	2 (7.7)	3 (7.0)	4 (8.5)
Confirmed iORR, N (%) [b]	14 (77.8)	6 (28.6)	15 (60.0)	2 (7.7)	29 (67.4)	8 (17.0)
(95% CI)	(52.36, 93.59)	(11.28, 52.18)	(38.67, 78.87)	(0.95, 25.13)	(51.46, 80.92)	(7.65, 30.81)
Odds ratio (95% CI) [c]	10.42 (1.90, 57.05)		15.00 (2.96, 75.95)		13.00 (4.38, 38.61)	
P-value [c]	0.0028		<0.0001		<0.0001	
iORR (confirmed + unconfirmed), N (%) [d]	15 (83.3)	7 (33.3)	19 (76.0)	4 (15.4)	34 (79.1)	11 (23.4)
(95% CI)	(58.58, 96.42)	(14.59, 56.97)	(54.87, 90.64)	(4.36, 34.87)	(63.96, 89.96)	(12.30, 38.03)
Odds ratio (95% CI) [c]	9.29 (1.88, 45.85)		19.57 (4.27, 89.67)		16.30 (5.32, 49.92)	
P-value [c]	0.0023		<0.0001		<0.0001	

Source: Study 301 Table 15.2.3.1.1, 15.2.3.2.1, 15.2.3.1.3, 15.2.3.2.3, 15.2.3.1.5, and 15.2.3.2.5 (data cutoff: 19 February 2018).
Abbreviations: BIRC, blinded independent review committee; CR, complete response; iCNS, intracranial central nervous system; iORR, intracranial objective response rate; NE, not estimable; PD, progressive disease; PR, partial response.
a Includes subjects who had nonmeasurable disease at baseline by BIRC, died early, or with unknown response.
b Confirmed iORR was defined as the proportion of subjects who achieved confirmed intracranial CR or PR.
c Odds ratios and p-values were from a Cochran-Mantel-Haenszel test stratified by presence of prior chemotherapy for locally advanced or metastatic disease at study entry.
d iORR is defined as the proportion of subjects who achieved confirmed or unconfirmed intracranial CR or PR.

Table 61: BIRC-Assessed iPFS by Baseline iCNS Metastases and for the Full ITT Population

Baseline CNS Metastases:	Any		None		Full ITT Population	
	Arm A Brigatinib (N = 43)	Arm B Crizotinib (N = 47)	Arm A Brigatinib (N = 94)	Arm B Crizotinib (N = 91)	Arm A Brigatinib (N = 137)	Arm B Crizotinib (N = 138)
N with events (%)	11 (25.6)	28 (59.6)	11 (11.7)	11 (12.1)	22 (16.1)	39 (28.3)
Death	0	2 (4.3)	9 (9.6)	4 (4.4)	9 (6.6)	6 (4.3)
PD	10 (23.3)	24 (51.1)	2 (2.1)	7 (7.7)	12 (8.8)	31 (22.5)
Palliative radiotherapy to the brain	1 (2.3)	2 (4.3)	0	0	1 (0.7)	2 (1.4)
N censored (%)	32 (74.4)	19 (40.4)	83 (88.3)	80 (87.9)	115 (83.9)	99 (71.7)
iPFS						
Median, months	NE	5.585	NE	NE	NE	NE
(95% CI)	(10.97, NE)	(4.07, 9.17)	(NE, NE)	(NE, NE)	(NE, NE)	(11.07, NE)
KM estimate, %						
(95% CI) [N at risk]	66.7	20.8	84.1	81.7	78.0	61.1
12 months	(47, 80)	(6, 42)	(72, 91)	(68, 90)	(68, 85)	(50, 71)
	[N = 9]	[N = 2]	[N = 18]	[N = 15]	[N = 27]	[N = 17]
Log-rank p-value [a]	<0.0001		0.9274		0.0006	
HR	0.265		0.960		0.415	
(95% CI) [a]	(0.13, 0.54)		(0.42, 2.22)		(0.24, 0.70)	
P-value [a]	0.0002		0.9234		0.0011	

Source Study 301 Table 15.2.4.1.1, 15.2.4.1.2, and 15.2.4.1.4 (data cutoff: 19 February 2018).
Abbreviations: BIRC, blinded independent review committee; HR, hazard ratio; iCNS, intracranial central nervous system; iPFS, intracranial progression-free survival, ITT, intent-to-treat; KM, Kaplan-Meier; NE, not estimable; PD, progressive disease.
a Brigatinib vs. crizotinib
P-values from a log-rank test stratified by presence of intracranial central nervous system metastases at baseline and prior chemotherapy for locally advanced or metastatic disease at study entry. The HR and associated p-value were obtained using a Cox proportional hazards model with randomization stratification factors as covariates.

Table 62: BIRC-Assessed Time to Intracranial Response and iDOR for Patients with Baseline iCNS Metastases

Baseline iCNS Metastases:	Measurable		Any	
	Arm A Brigatinib (N = 18)	Arm B Crizotinib (N = 21)	Arm A Brigatinib (N = 43)	Arm B Crizotinib (N = 47)
Number with confirmed response (%)	14 (77.8)	6 (28.6)	29 (67.4)	8 (17.0)
Number censored (%)	10 (71.4)	3 (50.0)	24 (82.8)	5 (62.5)
Time to response (in confirmed responders)				
Median, months (95% CI)	1.856 (1.77, 3.55)	1.791 (0.79, 1.87)	1.873 (1.87, 3.61)	1.823 (0.79, 5.72)
iDOR (in confirmed responders)				
Median, months (95% CI)	NE (4.50, NE)	9.232 (3.88, 9.23)	NE (NE, NE)	9.232 (3.88, 9.23)
KM estimate, % (95% CI) [N at risk]				
12 months	60.8 (25, 84) [N = 1]	NE (NE, NE) [N = 0]	75.8 (50, 89) [N = 3]	NE (NE, NE) [N = 0]

Source: Study 301 Table 15.2.7.4 and 15.2.7.2 (data cutoff: 19 February 2018).
Abbreviations: BIRC, blinded independent review committee; iCNS, intracranial central nervous system; iDOR, intracranial duration of response; KM, Kaplan-Meier.

2.2.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy assessment is based on three studies:

Study 101 is an ongoing phase 1/2 study which included an evaluation of anti-tumour activity. This open-label study included a dose-escalation phase followed by expansion cohorts, and provided some data relevant to the target population at the proposed dose.

Study 201 is the pivotal study for this application. This is an ongoing open-label multicentre phase 2 study in patients with advanced ALK+ NSCLC previously treated with crizotinib. The eligibility criteria were appropriate. Patients were randomised 1:1 to brigatinib 90 mg QD or brigatinib 180 mg QD with a 7 day lead-in at 90 mg QD (90/180 mg) until disease progression or intolerable toxicity. The initially recommended phase 2 dose (RP2D) was determined to be 180 mg QD, but the dose was changed due to acute dose-related early onset pulmonary events. Therefore, the phase II study was designed to test two dosing regimens.

There were a number of protocol amendments and deviations; however, these do not affect the interpretation of the study results. The chosen endpoints are appropriate for a phase 2 study.

Although this is a randomised study, no placebo or active comparator arm has been included. The comparison of the proposed 90/180 mg dose against the 90 mg dose provides some evidence of efficacy in terms of dose response, but it should be noted that the study was not powered for statistical comparison between the treatment arms regarding differences in efficacy as the purpose was to assess the potential dose effect.

During the procedure, the applicant submitted top-line results from the ongoing phase 3 study (AP-26113-13-301), comparing brigatinib and crizotinib in the first-line setting.

Efficacy data and additional analyses

In **study 101**, a total of 137 advanced cancer patients were enrolled and dosed, including 79 patients with ALK+ NSCLC, of which 71 had been treated with crizotinib. A total of 50 ALK+ NSCLC patients had brain metastases at baseline. The 90 mg/180 mg cohort included 25 patients with ALK+ NSCLC previously treated with crizotinib, and therefore of relevance for this application. In this group, 19/25 patients (76.0%; 95% CI: 54.9%, 90.6%) had a confirmed objective response. The median time to response was 1.9 months (range 1.2 – 6.0 months). The KM estimate median duration of response

was 26.1 months (95% CI: 7.9, 26.1). The KM estimate of median PFS was 16.3 months (95% CI: 9.2, not reached). Median overall survival (KM estimate) was not reached in this group. Of those with ALK+ NSCLC previously treated with crizotinib in the 90/180 mg QD group, there were 18 evaluable patients with brain metastases at baseline, of which 8 (44.4%; 95% CI: 21.5%, 69.2%) had a confirmed response by IRC. The KM estimate median intracranial duration of response was 11.4 months (95% CI: 5.6, 11.4) and the KM estimate median intracranial PFS was not reached.

In study 201, a total of 222 patients were randomised to brigatinib 90 mg (n=112) or brigatinib 90/180 mg (n=110). Around half were European. At the 29 September 2017 data extraction, 26.6% remain in study treatment overall. The median follow-up time is 24.3 months. The phase 2 results are considered mature and robust.

For the primary outcome of confirmed ORR by investigator assessment in the ITT population, the rate was 45.5% (97.5% CI: 34.8, 56.5) for the 90 mg group compared to 56.4% (97.5% CI: 45.2, 67.0) for the 90/180 mg group. Confirmed CR by investigator assessment was also increased for the 90/180 mg group: 4.5% vs 1.8%. The ORR by IRC were in line, however the CR was higher in the 90 mg group assessed by IRC (5.4%).

The median time to response was 1.8 to 1.9 months. The updated KM estimate median investigator-assessed duration of response was 12.0 months (95% CI: 9.2, 17.7) for patients in the 90 mg group and 13.8 months (95% CI: 10.2, 19.3) for patients in 90/180 mg group.

IRC assessed duration of response was in line. Therefore, responses appear rapid and are durable. The updated KM estimate median PFS was 9.2 months (95% CI: 7.4, 11.1) for the 90 mg group and 15.6 months (95% CI: 11.1, 21.0) for the 90 mg/180 mg group. PFS results by IRC were also in line. PFS is considered more clinically meaningful for patients than ORR. The median PFS estimate for the proposed 90/180 mg QD regimen is significantly longer than that estimated for the lower dose of 90 mg QD, whether investigator or IRC-assessed.

The median OS estimate for brigatinib is 34.1 months (95% CI 27.7-NR) in the 90/180 mg group, which is considered encouraging in this post-crizotinib second-line setting. Of note, the median OS for crizotinib as first-line treatment is 20.3 months.

It is acknowledged that patients with brain metastases have a special medical need for efficacy in the CNS and that it poses a major problem after crizotinib as approximately 60% of patients are afflicted at the time of second-line treatment. Brigatinib has shown promising efficacy in the CNS, especially regarding the intracranial PFS of 18.4 months for patients with ANY brain metastases at baseline (n=73, measurable and non-measurable only). For patients with measurable brain metastases at baseline (n=12), the ORR is 66.7% (95% CI: 41-86.6). The median duration of intracranial response of 16.6 months may be considered unreliable due to the small sample size. However, based on the KM estimates, over half of responders maintained response for at least 12 months.

Subgroup analyses for investigator assessed ORR were generally in line with the overall outcome, bearing in mind that some subgroups are small. There appeared to be improved outcomes for the subgroup with a best response to crizotinib of CR/PR compared to other/unknown: 65.8% vs 32.4%. It might be expected that tumours sensitive to crizotinib are more likely to be sensitive to brigatinib.

Patients who never smoked and were former smokers had no clinically significant impact on confirmed ORR. However, although numbers are limited, out of the 10 patients who were current smokers, none had an objective response to treatment and this may be an important signal. On that basis, the Applicant should analyse the future collected data on this patient population (current smokers) in the ongoing 301 study and report them as part of the post-authorisation commitment (Annex II).

Overall, the adjusted (for baseline scores) mean scores for the transformed Global Health Status/QOL Scale increased over time up to cycle 7, and tailed off slightly from then onwards, although at cycle 18, means remained above baseline levels. There was no difference between treatment groups. Hence, there were no detrimental effects on quality of life in the pivotal study compared to baseline.

In order to select patients most likely to benefit from treatment, it is important to have an understanding of genetic biomarkers such as secondary mutations in the ALK kinase domain that could predict response to brigatinib (or inform subsequent treatment options). The Sponsor planned to collect tissue samples at baseline (after progression on crizotinib), and where possible after progression on brigatinib, for analysis by next genome sequencing (NGS). However, only 17 baseline samples out of a possible 222 samples were evaluable. The Applicant has provided available data on resistance mutations before and after brigatinib, however the clinical data are still limited. During the procedure, data from the expanded access program was also submitted in support of the efficacy of brigatinib (data not shown). Eleven ALK+ NSCLC patients previously treated with alectinib have received brigatinib. Treatment outcomes are reported by the Applicant, based on physician assessments. Three patients who had progressed on alectinib responded to brigatinib (1 CR, 2 PR). This data, although less robust than clinical trial data, suggests that brigatinib may overcome some resistance mechanisms associated with alectinib. It is currently premature to conclude on the actual clinical use of these results. However, it is endorsed that the Applicant is collecting tumour and plasma samples from patients enrolling in the phase 3 study, as these data may be key in the future handling of ALK-positive patients both up front and in the case of progression. The applicant should submit these data post-authorisation (Annex II).

The Applicant has submitted top-line results from the ongoing phase 3 study (AP26113-13-301), comparing brigatinib and crizotinib in the first-line setting.

The design, dosing and endpoints are generally endorsed; however, the allowance of crossover for the patients receiving crizotinib makes the interpretation of the OS results more difficult.

The median duration of follow-up is considered short, with 11 and 9.3 months follow-up in each arm.

The planned IA shows results after 26.3% events in arm A and 45.7% events in arm B. The analysis met the predefined number of events (103) assessed by the investigator, and there were significantly more events in patients receiving crizotinib. The PFS HR of 0.492 (95% CI: 0.33, 0.74) between the arms is statistically significant and clinically relevant.

Confirmed ORR by BIRC was 70.8% for brigatinib vs 60.1% for crizotinib. Confirmed complete response was 3.6% for brigatinib vs 5.1% for crizotinib. The preliminary results from phase 3 confirm the mature efficacy data observed in phase 2. The median DOR was only reached with crizotinib (~11 months) although there were 97 and 83 patients in arm A and B, respectively, who were evaluable, indicating a longer duration of response with brigatinib. The OS data is not mature for assessment at this point in time, although no evidence for detrimental effect on survival is observed.

Intracranial efficacy are assessable for a limited number of patients with measurable CNS metastases, i.e. 18 and 21 patients in arm A and B, respectively. For these patients confirmed intracranial ORR was 14/18 (77.8%) and 6/21 (28.6%) for brigatinib and crizotinib, respectively. Median intracranial DOR was NE in the brigatinib arm and 9.2 months in the crizotinib arm. Although numbers are small, the difference in intracranial ORR suggests that brigatinib is associated with increased intracranial activity compared to crizotinib, supporting its efficacy in second line. The results are also consistent when evaluating the full ITT population, where there are very few intracranial PFS events with brigatinib (16.1%) compared to arm B (28.3%).

The applicant is requested to submit the final CSR of study AP26113-13-301 to further characterise the efficacy and safety of brigatinib which is currently based on data which requires confirmation of previous efficacy assumptions (see Annex II)

2.2.3. Conclusions on the clinical efficacy

The efficacy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib is demonstrated on the basis of high ORR and long duration of response.

The CHMP considers the following measures necessary to address issues related to efficacy:

In order to further characterise the efficacy and safety of brigatinib in the treatment of patients with ALK-positive NSCLC, the MAH should submit the clinical study report of the phase III study AP26113-13-301 comparing brigatinib versus crizotinib in patients with advanced ALK+ NSCLC who have not previously received ALK-directed therapy.

2.3. Clinical safety

The clinical safety database is primarily derived from two studies, a phase 1/2 study (**101**) and a phase 2 study (**201**). The data extraction date for both studies was 31 May 2016 however updated safety data from the 201 study are based on the 29 September 2017 data extraction. Study 201 only included patients with advanced ALK+ NSCLC who had received prior crizotinib; 110 patients were treated at the proposed dose. Therefore, study 201 provides the primary basis for the safety evaluation in ALK+ NSCLC previously treated with crizotinib.

Study **AP26113-13-301 (study 301)** is an ongoing, phase 3, randomized, multicentre study to evaluate the efficacy and safety of brigatinib in patients with advanced ALK+ NSCLC who have not previously received ALK-directed therapy. During the procedure, the applicant submitted safety data from the 301 study, based on a data extraction date of 19 February 2018.

The brigatinib **expanded access programs (EAPs)** were initiated in both Europe and US in 2016 for patients with locally advanced or metastatic ALK+ NSCLC with disease that has progressed during treatment with or is intolerant to at least one prior ALK inhibitor. The safety data from the EAPs (n=61) consists of reported SAEs, based on a data extraction date of 16 October 2016.

Patient exposure

Table 63: Exposure of patients with ALK+ NSCLC (cut-off: 19/02/2018[%])

	Patients enrolled	Patients exposed	Patients exposed to the proposed dose range	Patients exposed to the proposed dose range for 6 to < 12 months	Patients exposed to the proposed dose range for ⩾ 12 months
Placebo-controlled	N/A	-	-	-	-
Active –controlled	275	273	136	72	33
Open studies	301	298	138	45	61
Post marketing	N/A	-	-	-	-
Compassionate use[$]	61	61	Not known	Not known	Not known

* In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.
[%]Cut-off is 19/02/2018 for study 301

A study population of 138 patients from phase 2 and 136 patients from phase 3 with ALK+ NSCLC have been exposed to brigatinib at the proposed dose of 90 mg QD for 7 days, then 180 mg QD. A safety analysis has been submitted with a median follow up of 17.9 months.

Table 64: Overall Extent of Exposure in Patients with Advanced Malignancies by Brigatinib Starting Dose by Study AP26113-11-101 - Safety Population

	Study AP26113-11-101		
	90 mg QD ALK+ NSCLC[a] (N=14)	90 mg QD → 180 mg QD ALK+ NSCLC[a] (N=28)	All Patients (N=137)
Duration of Exposure (days)			
n	14	28	137
Mean (SD)	509.5 (353.30)	572.9 (324.67)	433.0 (429.82)
Median	483.0	667.0	227.0
Min, Max	5, 1430	1, 988	1, 1443
Duration of Exposure [n (%)]			
<1 month	1 (7.1)	2 (7.1)	20 (14.6)
1 - <3 mos	0	2 (7.1)	26 (19.0)
3 - <6 mos	1 (7.1)	1 (3.6)	15 (10.9)
6 - <12 mos	4 (28.6)	3 (10.7)	19 (13.9)
≥12 mos	8 (57.1)	20 (71.4)	57 (41.6)
Number of Days Dosed			
n	14	28	137
Mean (SD)	512.6 (351.54)	560.5 (321.01)	423.2 (422.13)
Median	479.0	666.0	226.0
Min, Max	5, 1399	1, 978	1, 1402
Observed Total Dose (mg)			
n	14	28	137
Mean (SD)	63154.3 (61475.51)	93223.9 (56864.58)	68341.8 (74534.66)
Median	43110.0	85920.0	35730.0
Min, Max	450, 242100	90, 170490	90, 335760
Dose Intensity (mg/day)			
n	14	28	137
Mean (SD)	111.9 (34.47)	158.9 (36.69)	152.1 (50.28)
Median	89.9	177.3	170.7
Min, Max	88, 187	80, 208	19, 300
Relative Dose Intensity (%)[b]			
n	14	28	137
Mean (SD)	117.1 (47.05)	89.1 (19.98)	92.0 (27.72)
Median	99.6	99.6	98.2
Min, Max	21, 208	50, 116	7, 208

Source: Study AP26113-11-101 Tables 14.3.1.1.1 (Data Extraction Date: 31 May 2016);
Study AP26113-13-201 Table 14.3.1.1.1 (Data Extraction Date: 31 May 2016)
Abbreviations: ALK+ = anaplastic lymphoma kinase positive; NSCLC = non-small cell lung cancer; QD = once a day;
SD = standard deviation. [a]with/without prior crizotinib treatment. [b]relative to starting dose with escalation allowed

Table 65: Study 201 Drug Exposure (Treated Population). Data extraction date (29/09/2017)

	Arm A 90 mg QD N = 109	Arm B 90 mg QD→ 180 mg QD N = 110	Total N = 219
Duration of exposure (days) [a]			
Mean (SD)	454.6 (331.42)	504.4 (335.20)	479.7 (333.49)
Median	402.0	522.0	469.0
Minimum, maximum	1, 1066	2, 1193	1, 1193
Duration of exposure, n (%)			
<1 month	5 (4.6)	8 (7.3)	13 (5.9)
1 to <3 months	16 (14.7)	6 (5.5)	22 (10.0)
3 to <6 months	10 (9.2)	12 (10.9)	22 (10.0)
6 to <12 months	20 (18.3)	20 (18.2)	40 (18.3)
≥12 months	58 (53.2)	64 (58.2)	122 (55.7)
Number of days dosed			
Mean (SD)	447.7 (328.84)	492.0 (329.90)	470.0 (329.37)
Median	402.0	516.0	443.0
Minimum, maximum	1, 1066	2, 1130	1, 1130
Observed total dose (mg)			
Mean (SD)	44922.7 (35392.91)	78467.5 (54522.18)	61771.6 (48882.66)
Median	39690.0	75780.0	52290.0
Minimum, maximum	90, 151740	180, 183870	90, 183870
Dose intensity (mg/day)			
Mean (SD)	96.8 (20.03)	151.5 (34.46)	124.3 (39.31)
Median	90.0	168.8	118.4
Minimum, maximum	56, 173	39, 179	39, 179
Relative dose intensity (%) [b]			
Mean (SD)	107.5 (22.26)	88.4 (17.24)	97.9 (22.05)
Median	100.0	98.2	99.5
Minimum, maximum	63, 193	33, 101	33, 193
Any dose adjustment, n (%)			
Yes	45 (41.3)	71 (64.5)	116 (53.0)
No	64 (58.7)	39 (35.5)	103 (47.0)
Dose reduction due to AE, n (%)			
Yes	8 (7.3)	32 (29.1)	40 (18.3)
No	101 (92.7)	78 (70.9)	179 (81.7)
Dose interruption of ≥3 days, n (%)			
Yes	39 (35.8)	60 (54.5)	99 (45.2)
No	70 (64.2)	50 (45.5)	120 (54.8)
Dose interruption due to AE			
Yes	45 (41.3)	68 (61.8)	113 (51.6)
No	64 (58.7)	42 (38.2)	106 (48.4)
Duration of longest dose interruption ≥3 days	N=39	N=60	N=99
Mean (SD)	11.7 (7.21)	12.7 (8.59)	12.3 (8.05)
Median	9.0	10.5	10.0
Minimum, maximum	3, 31	3, 45	3, 45

Source: Table 14.3.1.1 (Data extraction date: 29 September 2017).
Abbreviations: AE, adverse event; QD, once daily.
N = 109 (Arm A), 110 (Arm B), and 219 (Total) unless otherwise specified.
[a] Days from first dose to last dose.
[b] Observed total dose divided by expected total dose times 100. Relative dose intensity can exceed 100% in Arm A if a patient had dose escalation after disease progression, and in Arm B when patients escalate to 180 mg before Day 8.

Table 66: Duration of Exposure. Studies AP26003-11-101 and AP26113-13-201. By Phase 2 Doses and All Patients. Safety Population. Database Cutoff Date: 2017-09-29

	90 QD (N=123)	90 to 180 QD (N=138)	Total (N=356)
Duration of Exposure (months)[1]			
N	123	138	356
Mean (SD)	15.1 (10.94)	17.0 (10.94)	15.2 (12.27)
Median	13.2	17.4	12.1
Min, Max	0.0, 47.0	0.0, 39.2	0.0, 47.4

Adverse events

Table 67: Overview of TEAEs (Treated Population – Study 201)

	Number of Patients (%)		
	Arm A 90 mg QD (N = 109)	Arm B 90 mg QD→ 180 mg QD (N = 110)	Total (N = 219)
Patients with TEAEs	109 (100.0)	110 (100.0)	219 (100.0)
Drug related	89 (81.7)	105 (95.5)	194 (88.6)
Grade ≥3	69 (63.3)	78 (70.9)	147 (67.1)
Grade ≥3, drug related	26 (23.9)	50 (45.5)	76 (34.7)
TEAEs leading to treatment discontinuation	4 (3.7)	12 (10.9)	16 (7.3)
TEAEs leading to dose reduction	8 (7.3)	32 (29.1)	40 (18.3)
TEAEs leading to dose interruption	45 (41.3)	68 (61.8)	113 (51.6)
Patients with SAEs	54 (49.5)	62 (56.4)	116 (53.0)
Drug related	8 (7.3)	20 (18.2)	28 (12.8)
Grade ≥3	45 (41.3)	51 (46.4)	96 (43.8)
Deaths within 30 days after last dose or possibly related	21 (19.3)	11 (10.0)	32 (14.6)

Source: Study 201 Addendum 2 Table 14.3.2.1 and 14.3.2.5 (data cutoff: 29 September 2017).
Abbreviations: QD, once daily; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

In the 90/180 mg group of study 201 (data cut 29 September 2017), the most frequent AEs by preferred term (PT) were nausea (50%), diarrhoea (45.5%), cough (40.9%), blood CPK increased (35.5%), headache (39.1%), fatigue (34.5%), vomiting (34.5%), dyspnoea (45.5%), and hypertension (28.2%).

Table 68: Treatment-Emergent Adverse Events in ≥10% Patients Overall (Study AP26113-13-201 – treated population)

Preferred Term	Arm A 90 mg QD N = 109	Arm B 90 mg QD→ 180 mg QD N = 110	Total N = 219
Patients with ≥1 TEAE, n (%)	109 (100.0)	110 (100.0)	219 (100.0)
Nausea	45 (41.3)	55 (50.0)	100 (45.7)
Diarrhoea	32 (29.4)	50 (45.5)	82 (37.4)
Vomiting	42 (38.5)	38 (34.5)	80 (36.5)
Headache	36 (33.0)	43 (39.1)	79 (36.1)
Cough	32 (29.4)	45 (40.9)	77 (35.2)
Fatigue	31 (28.4)	38 (34.5)	69 (31.5)
Blood creatine phosphokinase increased	19 (17.4)	39 (35.5)	58 (26.5)
Decreased appetite	30 (27.5)	27 (24.5)	57 (26.0)
Dyspnoea	27 (24.8)	30 (27.3)	57 (26.0)
Constipation	29 (26.6)	25 (22.7)	54 (24.7)
Hypertension	20 (18.3)	31 (28.2)	51 (23.3)
Back pain	17 (15.6)	26 (23.6)	43 (19.6)
Muscle spasms	17 (15.6)	26 (23.6)	43 (19.6)
Abdominal pain	21 (19.3)	17 (15.5)	38 (17.4)
Arthralgia	19 (17.4)	19 (17.3)	38 (17.4)
Aspartate aminotransferase increased	15 (13.8)	22 (20.0)	37 (16.9)
Rash	12 (11.0)	23 (20.9)	35 (16.0)
Dizziness	16 (14.7)	18 (16.4)	34 (15.5)
Pyrexia	22 (20.2)	12 (10.9)	34 (15.5)
Alanine aminotransferase increased	15 (13.8)	18 (16.4)	33 (15.1)
Amylase increased	13 (11.9)	20 (18.2)	33 (15.1)
Asthenia	13 (11.9)	18 (16.4)	31 (14.2)
Lipase increased	11 (10.1)	20 (18.2)	31 (14.2)
Viral upper respiratory tract infection	14 (12.8)	15 (13.6)	29 (13.2)
Insomnia	18 (16.5)	10 (9.1)	28 (12.8)
Neoplasm progression	19 (17.4)	9 (8.2)	28 (12.8)
Pain in extremity	17 (15.6)	11 (10.0)	28 (12.8)
Paraesthesia	12 (11.0)	12 (10.9)	24 (11.0)
Pneumonia	6 (5.5)	18 (16.4)	24 (11.0)
Pruritus	10 (9.2)	13 (11.8)	23 (10.5)
Musculoskeletal pain	8 (7.3)	14 (12.7)	22 (10.0)
Myalgia	7 (6.4)	15 (13.6)	22 (10.0)
Oedema peripheral	10 (9.2)	12 (10.9)	22 (10.0)
Oropharyngeal pain	11 (10.1)	11 (10.0)	22 (10.0)
Upper respiratory tract infection	13 (11.9)	9 (8.2)	22 (10.0)

Source: Table 14.3.3.4.1 (data extraction date: 29 September 2017).
Abbreviations: QD, once daily; TEAE, treatment-emergent adverse event.
Percentages are based on the number of patients recorded. Patients may have more than 1 adverse event per Preferred Term at each level of patient summarization. A patient is counted once for the most severe event.

The most frequently reported ≥ Grade 3 AEs in the 90/180 mg group of study 201 (data cut 29 September 2017) (apart from neoplasm progression) were blood CPK increased (14.5%), hypertension (10%), and pneumonia (5.5%). Although GI AEs are reported frequently, there were no ≥ Grade 3 events in ≥ 2% of the population. Therefore, GI toxicity appears to be manageable, with a low frequency of severe events, and no discontinuations.

Table 69: Grade ⩾3 TEAEs Occurring in ⩾2% of Patients Overall (Study AP26113-13-201 – Treated Population)

Preferred Term	Arm A 90 mg QD N = 109	Arm B 90 mg QD → 180 mg QD N = 110	Total N = 219
Patients with at least 1 Grade ≥3 TEAE, n (%)	69 (63.3)	78 (70.9)	147 (67.1)
Neoplasm progression	18 (6.5)	9 (8.2)	27 (12.3)
Blood creatine phosphokinase increased	5 (4.6)	16 (14.5)	21 (9.6)
Hypertension	6 (5.5)	11 (10.0)	17 (7.8)
Lipase increased	5 (4.6)	6 (5.5)	11 (5.0)
Pneumonia	4 (3.7)	6 (5.5)	10 (4.6)
Malignant pleural effusion	3 (2.8)	4 (3.6)	7 (3.2)
Pneumonitis	3 (2.8)	4 (3.6)	7 (3.2)
Neutrophil count decreased	4 (3.7)	2 (1.8)	6 (2.7)
Dyspnoea	3 (2.8)	2 (1.8)	5 (2.3)
Hyponatremia	2 (1.8)	3 (2.7)	5 (2.3)
Rash	1 (0.9)	4 (3.6)	5 (2.3)

Source: Table 14.3.3.5 (data extraction date: 29 September 2017).
Abbreviations: QD, once daily; TEAE, treatment-emergent adverse event.
Percentages are based on the number of patients recorded. Patients may have more than 1 adverse event per Preferred Term at each level of patient summarization. A patient is counted once for the most severe event.

Adverse drug reactions

The methodology for the identification and presentation of adverse drug reactions (ADRs) is presented below:

- Pooled safety data from Study AP26113-13-201 (data extraction: 29 September 2017) and Study AP26113-11-101 (data extraction: 31 May 2016) at the recommended dose of 90 mg QD→ 180 mg QD was used for the ADRs determination.
- All treatment related adverse events were reviewed and PTs reported at ≥ 2% in either treatment regimen [90 mg (n=123) or 90 mg QD→ 180 mg QD (n=138)] were determined as ADRs.

  Actual frequencies of these ADRs were based on frequencies of treatment emergent adverse events (pooled data) at the recommended dose (90 mg QD→ 180 mg QD regimen) (n=138). The ADR table was created considering both these parameters of treatment related adverse events involving percentages from treatment emergent pooled table.
- The frequency categories in the tabulated list of adverse reactions for events fulfilling the causality requirement of ADR were based on the frequencies of all causality AEs (irrespectively of investigators' assessments) to minimize bias.
- ADRs associated with chemistry and haematology laboratory abnormalities were identified using laboratory shift from normal/baseline tables. A laboratory abnormality was included as an ADR if the overall shift from normal/baseline (all grades) percentage was ≥20% in either arm.

Table 70: Adverse reactions reported in patients treated with Brigatinib in ALTA and Study 101 (per Common Terminology Criteria for Adverse Events (CTCAE) version 4.0) at the 180 mg regimen

System organ class	Frequency category	Adverse reactions* all grades	Adverse reactions grade 3-4
Infections and infestations	Very common	Pneumonia[a] (15%) Upper respiratory tract infection (13%)	
	Common		Pneumonia[a] (4%)
Blood and lymphatic system disorders	Very common	Anemia (52%) Lymphocyte count decreased (50%) APTT increased (36%) White blood cell count decreased (27%) Neutrophil count decreased (15%) Decreased platelet count (11%)	Lymphocyte count decreased (20%)
	Common		APTT increased (2%) Anemia (1%) Neutrophil count decreased (1%)
Metabolism and nutrition disorders	Very common	Hyperglycemia (66%) Hyperinsulinemia[b] (61%) Hypophosphatemia (38%) Decreased appetite (25%) Hypokalemia (24%) Hypomagnesemia (23%) Hyponatremia (23%) Hypercalcemia (20%)	
	Common		Hypophosphatemia (9%) Hyperglycemia (6%) Hyponatremia (4%) Hypokalemia (1%) Decreased appetite (1%)
Psychiatric disorders	Very common	Insomnia (11%)	
Nervous system disorders	Very common	Headache[c] (44%), Peripheral neuropathy[d] (28%) Dizziness (16%)	
	Common	Memory Impairment (7%) Dysgeusia (5%)	Peripheral neuropathy[d] (2%) Headache[c] (1%)
Eye disorders	Very common	Visual Disturbance[e] (20%)	
	Common		Visual disturbance[e] (2%)
Cardiac disorders	Common	Tachycardia[f] (6%) Electrocardiogram QT prolonged (6%) Bradycardia[g] (5%) Palpitations (4%)	
	Uncommon		Electrocardiogram QT prolonged (0.7%)
Vascular disorders	Very Common	Hypertension (27%)	Hypertension (10%)
Respiratory, thoracic and mediastinal disorders	Very Common	Cough (41%) Dyspnea[h] (29%)	
	Common	Pneumonitis[i] (9%)	Pneumonitis[i] (4%) Dyspnoea[h] (3%)
Gastrointestinal disorders	Very common	Lipase increased (50%) Nausea (49%) Diarrhea[j] (46%) Amylase increased (44%) Vomiting (32%) Constipation (23%) Abdominal pain[k] (19%) Dry mouth (10%) Stomatitis[l] (10%)	Lipase increased (12%)
	Common	Dyspepsia (6%) Flatulence (3%)	Amylase increased (9%) Abdominal pain[k] (1%)

System organ class	Frequency category	Adverse reactions* all grades	Adverse reactions grade 3-4
	Uncommon	Pancreatitis (0.7%)	Nausea (0.7%) Dyspepsia (0.7%) Pancreatitis (0.7%)
Hepatobiliary disorders	Very common	AST increased (66%) ALT increased (46%) Alkaline phosphatase increased (39%)	
	Common	Blood lactate dehydrogenase increased (8%) Hyperbilirubinaemia (7%)	ALT increased (4%) AST increased (3%) Alkaline phosphatase increased (2%) Hyperbilirubinaemia (1%)
Skin and subcutaneous tissue disorders	Very Common	Rash[m] (35%) Pruritus (13%)	
	Common	Dry skin (4%) Photosensitivity reaction (4%)	Rash[m] (4%) Photosensitivity reaction (1%)
	Uncommon		Dry skin (0.7%)
Musculoskeletal and connective tissue disorders	Very common	Blood CPK increased (50%) Myalgia[n] (41%) Arthralgia (21%) Musculoskeletal chest pain (10%)	Blood CPK increased (14%)
	Common	Pain in extremity (9%) Musculoskeletal stiffness (1%)	Pain in extremity (1%)
	Uncommon		Myalgia[n] (0.7%)
Renal and urinary disorders	Very common	Blood creatinine increased (17%)	
General disorders and administration site conditions	Very common	Fatigue[o] (48%) Edema[p] (17%) Pyrexia (12%)	
	Common	Pain (5%) Non-cardiac chest pain (4%) Chest discomfort (4%)	Fatigue[o] (2%)
	Uncommon		Non-cardiac chest pain (0.7%) Pyrexia (0.7%)
Investigations	Common	Weight decreased (7%)	
	Uncommon		Weight decreased (0.7%)

[a] Includes atypical pneumonia, pneumonia, pneumonia aspiration, pneumonia pseudomonal, lower respiratory tract infection, lower respiratory tract infection viral, lung infection
[b] Grade not applicable
[c] Includes headache, sinus headache, head discomfort, migraine, tension headache
[d] Includes paresthesia, peripheral sensory neuropathy, dysesthesia, hyperesthesia, hypoesthesia, neuralgia, neuropathy peripheral, neurotoxicity, peripheral motor neuropathy, polyneuropathy
[e] Includes altered visual depth perception, asthenopia, cataract, color blindness acquired, diplopia, glaucoma, intraocular pressure increased, macular edema, photophobia, photopsia, retinal edema, vision blurred, visual acuity reduced, visual field defect, visual impairment, vitreous detachment, vitreous floaters, amaurosis fugax
[f] Includes sinus tachycardia, tachycardia
[g] Includes bradycardia, sinus bradycardia
[h] Includes dyspnea, dyspnea exertional
[i] Includes interstitial lung disease, pneumonitis
[j] Includes diarrhea, diarrhea infectious
[k] Includes abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper, epigastric discomfort
[l] Includes aphthous stomatitis, stomatitis, aphthous ulcer, mouth ulceration, oral mucosal blistering
[m] Includes dermatitis acneiform, erythema, exfoliative rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, dermatitis, dermatitis allergic, generalised erythema, rash follicular, urticaria
[n] Includes musculoskeletal pain, myalgia, muscle spasms, muscle tightness, muscle twitching, musculoskeletal discomfort
[o] Includes asthenia, fatigue
[p] Includes eyelid edema, face edema, localised edema, edema peripheral, periorbital edema, swelling face, generalised edema, peripheral swelling
*The frequencies for ADR terms associated with chemistry and hematology laboratory changes were determined based on the frequency of abnormal laboratory shifts from baseline.

Serious adverse event / deaths / other significant events

Deaths

In study 201 and 101, respectively 12 and 10 patient deaths within 30 days of the last dose were not lung cancer-related. Based on patient narratives, 1 out of the 12 deaths in study 201 and 5 out of the 10 deaths in study 101 is possibly related to brigatinib.

Brigatinib-related early-onset pulmonary events (EOPEs) may have contributed to the deaths of 4 patients, of which 3 patients from study 101 were on doses higher than that proposed (90/180 mg) at the onset of the event.

Table 71: Summary of All Patients Deaths by Treatment Arm. Treated Population. Study No. AP26113-13-201

Cause of Death	ARM A (90 MG) (N=109)	ARM B (90/180 MG) (N=110)	Total (N=219)
Subjects Who Died	50 (45.9)	40 (36.4)	90 (41.1)
Disease/Neoplasm Progression	27 (24.8)	22 (20.0)	49 (22.4)
Lung Cancer†	4 (3.7)	8 (7.3)	12 (5.5)
Pneumonia	2 (1.8)	2 (1.8)	4 (1.8)
Death Reason From Survival Follow-Up Unknown†	0	3 (2.7)	3 (1.4)
Non Small Cell Lung Cancer†	2 (1.8)	0	2 (0.9)
Non-Small Cell Lung Cancer†	2 (1.8)	0	2 (0.9)
Respiratory Failure†	2 (1.8)	0	2 (0.9)
Unknown	1 (0.9)	1 (0.9)	2 (0.9)
Cerebral Ischaemia	1 (0.9)	0	1 (0.5)
Cerebrovascular Accident	1 (0.9)	0	1 (0.5)
Cognitive Disorder	0	1 (0.9)	1 (0.5)
Lung Cancer With Brain Metasasis	1 (0.9)	0	1 (0.5)
Malignancy	1 (0.9)	0	1 (0.5)

* denotes an absolute difference of at least 10% between the two arms; † denotes a relative increase of 50% for Arm A vs. Arm B or Arm B vs. Arm A when there was a difference in frequency of at least two events
[1] Includes causes of death from survival follow-up that are not coded preferred terms

Source: Dataset: (ADSL), Program: t_death.sas, Output: t_14_03_02_06_death.rtf, Generated on:14JUN2018 at 05:28, Data Cutoff: 29SEP2017

Table 72: TEAEs leading to deaths within 30 days after last dose or related to study drug (treated population) - Study AP26113-13-201

Preferred Term	Arm A 90 mg QD N = 109	Arm B 90 mg QD→ 180 mg QD N = 110	Total N = 219
Any TEAE leading to death, n (%)	21 (19.3)	11 (10.0)	32 (14.6)
Neoplasm progression	12 (11.0)	8 (7.3)	20 (9.1)
Pneumonia	2 (1.8)	1 (0.9)	3 (1.4)
Cognitive disorder	0	1 (0.9)	1 (0.5)
Malignant pleural effusion	1 (0.9)	0	1 (0.5)
Meningitis bacterial	1 (0.9)	0	1 (0.5)
Peritonitis	1 (0.9)	0	1 (0.5)
Pneumonia aspiration	1 (0.9)	0	1 (0.5)
Pulmonary embolism	1 (0.9)	0	1 (0.5)
Respiratory failure	1 (0.9)	0	1 (0.5)
Sudden death	0	1 (0.9)	1 (0.5)
Urosepsis	1 (0.9)	0	1 (0.5)

Source: Table 14.3.2.5 (data extraction date: 29 September 2017).
Abbreviations: QD, once daily; TEAE, treatment-emergent adverse event.

Serious adverse event

Table 73: Treatment-Emergent Serious Adverse Events occurring in ≥2% of Patients Overall - Study AP26113-13-201 (treated population)

Preferred Term	Arm A 90 mg QD N = 109	Arm B 90 mg QD→ 180 mg QD N = 110	Total N = 219
Patients with ≥1 serious TEAE, n (%)	54 (49.5)	62 (56.4)	116 (53.0)
Neoplasm progression	19 (17.4)	9 (8.2)	28 (12.8)
Pneumonia	4 (3.7)	10 (9.1)	14 (6.4)
Pneumonitis	2 (1.8)	9 (8.2)	11 (5.0)
Malignant pleural effusion	4 (3.7)	4 (3.6)	8 (3.7)
Dyspnoea	2 (1.8)	3 (2.7)	5 (2.3)

Source: Table 14.3.5.4 (data extraction date: 29 September 2017)
Abbreviations: QD, once daily; TEAE, treatment-emergent adverse event.
Percentages are based on the number of patients recorded. Patients may have more than 1 adverse event per Preferred Term at each level of patient summarization. A patient is counted once for the most severe event. Six of 9 patients in Arm B had pneumonitis that occurred during the first 7 days of treatment (ie, at brigatinib 90 mg QD). One patient in Arm A had disease progression at brigatinib 90 mg QD and was escalated to 180 mg QD; at >1 month after escalation, the patient had a TEAE of pneumonitis.

Adverse events of special interest

Pulmonary Adverse Events: Early Onset Pulmonary Events and Later Onset Pneumonitis Events

In study 201, 6.4% of patients experienced pulmonary adverse reactions of any grade, including ILD/pneumonitis, pneumonia and dyspnoea, early in treatment (within 9 days, median onset: 2 days); 2.7% of patients had Grade 3-4 pulmonary adverse reactions and 1 patient (0.5%) had fatal pneumonia. Following Grade 1-2 pulmonary adverse reactions, treatment with brigatinib was either interrupted and then restarted or the dose was reduced. Early pulmonary adverse reactions also occurred in study 101 (N = 137) including three fatal cases (hypoxia, acute respiratory distress syndrome and pneumonia).

Additionally, 2.3% of patients in study 201 experienced pneumonitis later in treatment, with 2 patients having Grade 3 pneumonitis.

Hepatic events

In study 201, elevations of ALT and AST were reported in 46% and 65% of patients treated with Alunbrig, respectively at the 180 mg regimen. For elevations to Grade 3 and 4, the incidences for ALT and AST were 5.5% and 3.6%, respectively.

No patients had dose reductions due to elevation of ALT or AST.

Elevated creatine phosphokinase

In study 201, elevations of CPK were reported in 50% of patients treated with Alunbrig at the 180 mg regimen. The incidence of Grade 3-4 elevations of CPK was 13.6%. The median time to onset for CPK elevations was 27 days. Dose reduction for CPK elevation occurred in 6.4% patients at the 180 mg regimen.

Pancreatic events

In study 201, elevations of amylase and lipase were reported in 43% and 50% of patients treated with Alunbrig, respectively at the 180 mg regimen. For elevations to Grade 3 and 4, the incidences for

amylase and lipase were 8.2% and 10%, respectively. The median time to onset for amylase elevations and lipase elevations was 17 days and 29 days, respectively. Dose reduction for elevation of lipase and amylase occurred in 1.8% and 0.9% of patients, respectively at the 180 mg regimen.

Peripheral neuropathy

In study 201, peripheral neuropathy adverse reactions were reported in 27.3% of patients treated at the 180 mg regimen.

Table 74: Treatment-emergent peripheral neuropathy adverse events sorted by preferred term by treatment arm - Treated population

Preferred Term	ARM A (90 MG) (N=109)	ARM B (90/180 MG) (N=110)	Total (N=219)
Subjects With At Least One Treatment-Emergent Peripheral Neuropathy Adverse Event	22 (20.2)	30 (27.3)	52 (23.7)
Paraesthesia	12 (11.0)	12 (10.9)	24 (11.0)
Peripheral Sensory Neuropathy	8 (7.3)	10 (9.1)	18 (8.2)
Hypoaesthesia	4 (3.7)	6 (5.5)	10 (4.6)
Neuralgia	2 (1.8)	1 (0.9)	3 (1.4)
Dysaesthesia†	0	2 (1.8)	2 (0.9)
Hyperaesthesia	1 (0.9)	1 (0.9)	2 (0.9)
Polyneuropathy	1 (0.9)	1 (0.9)	2 (0.9)
Neuropathy Peripheral	0	1 (0.9)	1 (0.5)
Neurotoxicity	0	1 (0.9)	1 (0.5)
Peripheral Motor Neuropathy	0	1 (0.9)	1 (0.5)

* denotes an absolute difference of at least 10% between the two arms; † denotes a relative increase of 50% for Arm A vs. Arm B or Arm B vs. Arm A when there was a difference in frequency of at least two events
Note: Percentages are based on the number of patients recorded. Patients may have more than one AE per preferred term at each level of patient summarization. A patient is counted once for the most severe event.
AEs were classified according to the most recent version of MedDRA available at the time of coding. Certain preferred terms have been regrouped for accuracy.
Peripheral Neuropathy Adverse Event defined by PTs: Dysaesthesia, Hyperaesthesia, Hypoaesthesia, Neuralgia, Neuropathy Peripheral, Neurotoxicity, Paraesthesia, Peripheral Motor Neuropathy, Peripheral Sensory Neuropathy, Polyneuropathy.

Data cutoff: 29Sept2017

Thirty (30) percent of patients had resolution of all peripheral neuropathy adverse reactions. The median duration of peripheral neuropathy adverse reactions was 4.5 months, with a maximum duration of 28.7 months.

Table 75: Duration in Months of Treatment-Emergent Peripheral Neuropathy Adverse Events Safety Population with Peripheral Neuropathy Adverse Events[a]

	ARM A (90 MG) (N=22)	ARM B (90/180 MG) (N=30)	TOTAL (N=52)
Duration of Peripheral Neuropathy Adverse Events (Month)			
N	22	30	52
Mean (SD)	5.7 (5.71)	8.7 (9.02)	7.4 (7.87)
Median	3.7	4.5	4.2
Min, Max	0.0, 19.1	0.0, 28.7	0.0, 28.7
< 3 months	10 (45.5%)	12 (40.0%)	22 (42.3%)
3 to < 6 months	5 (22.7%)	5 (16.7%)	10 (19.2%)
6 to < 12 months	3 (13.6%)	3 (10.0%)	6 (11.5%)
>= 12 months	4 (18.2%)	10 (33.3%)	14 (26.9%)

Source: AP26113-13-201 Table 14.3.8.5.1 (Data extraction date: 29Sept2017).

[a] Peripheral neuropathy adverse events were defined using Preferred Terms of Dysaesthesia, Hyperaesthesia, Hypoaesthesia, Neuralgia, Neuropathy Peripheral, Neurotoxicity, Paraesthesia, Peripheral Motor Neuropathy, Peripheral Sensory Neuropathy, Polyneuropathy.

Table 76: Summary of Resolution of Treatment-Emergent Peripheral Neuropathy Adverse Events Safety Population with Peripheral Neuropathy Adverse Events[a]

	ARM A (90 MG) (N=22)	ARM B (90/180 MG) (N=30)	TOTAL (N=52)
Outcome of Peripheral Neuropathy Adverse Events			
Subjects with resolution of all peripheral neuropathy adverse events [2], n(%)	11 (50.0%)	9 (30.0%)	20 (38.5%)
Subjects with resolution of at least one but not all peripheral neuropathy adverse events [3], n(%)	4 (18.2%)	6 (20.0%)	10 (19.2%)
Subjects with resolution of no peripheral neuropathy adverse events [4], n(%)	7 (31.8%)	15 (50.0%)	22 (42.3%)

Source: Study AP26113-13-201 Table 14.3.8.6.1 (Data extraction date: 29Sept2017).
[1] Peripheral neuropathy adverse events were defined using Preferred Terms of Dysaesthesia, Hyperaesthesia, Hypoaesthesia, Neuralgia, Neuropathy Peripheral, Neurotoxicity, Paraesthesia, Peripheral Motor Neuropathy, Peripheral Sensory Neuropathy, Polyneuropathy.
[2] Resolution of all events is defined as event status of resolved/recovered or resolved/recovered with sequelae for all events for a particular patient.
[3] Resolution of at least one but not all events is defined as event status of resolved/recovered or resolved/recovered with sequelae for at least one event per patient but not all events for the patient.
[4] Resolution of no events is defined as event status that has not reached resolved/recovered or resolved/recovered with sequelae for all events for a particular patient.

Visual disturbance

In study 201, visual disturbance adverse reactions were reported in 18% of patients treated with Alunbrig at the 180 mg regimen. Of these, three grade 3 adverse reactions (2.7%) including macular oedema and cataract were reported.

Dose reduction for visual disturbance occurred in two patients (1.8%) at the 180 mg regimen.

Table 77: Treatment-Emergent Vision Distrurbance Adverse Events Sorted by Descending Frequency of "Synonymm Recorded" Prefered Term By treatment Arm. Treated Population.

Preferred Term	ARM A (90 MG) (N=109)	ARM B (90/180 MG) (N=110)	Total (N=219)
Subjects With At Least One Treatment-Emergent Vision Disturbance Adverse Event†	13 (11.9)	20 (18.2)	33 (15.1)
Vision Blurred†	4 (3.7)	9 (8.2)	13 (5.9)
Diplopia	2 (1.8)	3 (2.7)	5 (2.3)
Visual Impairment†	1 (0.9)	4 (3.6)	5 (2.3)
Cataract†	0	3 (2.7)	3 (1.4)
Photopsia	2 (1.8)	1 (0.9)	3 (1.4)
Vitreous Floaters	2 (1.8)	1 (0.9)	3 (1.4)
Visual Acuity Reduced†	0	2 (1.8)	2 (0.9)
Amaurosis Fugax	0	1 (0.9)	1 (0.5)
Glaucoma	0	1 (0.9)	1 (0.5)
Macular Oedema	0	1 (0.9)	1 (0.5)
Photophobia	0	1 (0.9)	1 (0.5)
Retinal Oedema	0	1 (0.9)	1 (0.5)
Visual Field Defect	1 (0.9)	0	1 (0.5)
Vitreous Detachment	1 (0.9)	0	1 (0.5)

* denotes an absolute difference of at least 10% between the two arms; † denotes a relative increase of 50% for Arm A vs. Arm B or Arm B vs. Arm A when there was a difference in frequency of at least two events
Note: Percentages are based on the number of patients recorded. Patients may have more than one AE per preferred term at each level of patient summarization. A patient is counted once for the most severe event.
AEs were classified according to the most recent version of MedDRA available at the time of coding. Certain preferred terms have been regrouped for accuracy.
Vision Disturbance Adverse Event defined by PTs: Altered Visual Depth Perception, Amaurosis Fugax, Asthenopia, Cataract, Colour Blindness Acquired, Diplopia, Glaucoma, Intraocular Pressure Increased, Macular Oedema, Photophobia, Photopsia, Retinal Oedema, Vision Blurred, Visual Acuity Reduced, Visual Field Defect, Visual Impairment, Vitreous Detachment, Vitreous Floaters.

Source: Dataset: ADSL, ADAE, Program: t aenv.sas, Output: t 14 03 01 aenv.rtf, Generated on:17MAY2018 at 10:01, Data Cutoff: 29SEP2017

Hypertension

In study 201, hypertension was reported in 28% of patients treated with Alunbrig at the 180 mg regimen with 10% having Grade 3 hypertension. Dose reduction for hypertension occurred in 0.9% at the 180 mg regimen. Mean systolic and diastolic blood pressure, in all patients, increased over time.

Bradycardia

In study 201, bradycardia was reported in 4.5% of patients treated with Alunbrig at the 180 mg regimen.

Heart rates of less than 50 beats per minute (bpm) were reported in 8.2% of patients at the 180 mg regimen.

Laboratory findings

Table 78: Shift in Clinical Chemistry Laboratory Parameters from Baseline to Worst Value Post-Baseline in Terms of CTCAE Grades Studies AP26113-11-101 and AP26113-13-201. By Phase 2 Doses - Safety Population

	90 QD ALK+ NSCLC (N=123)	90 to 180 QD ALK+ NSCLC (N=138)	All Patients (N=356)
ALBUMIN/ DECREASED	12 (9.8)	17 (12.3)	47 (13.2)
ALKALINE PHOSPHATASE/ INCREASED	32 (26.0)	54 (39.1)	116 (32.6)
ALT (SGPT)/ INCREASED	56 (45.5)	63 (45.7)	153 (43.0)
AMYLASE/ INCREASED	40 (32.5)	60 (43.5)	146 (41.0)
APTT/ INCREASED	44 (35.8)	49 (35.5)	126 (35.4)
AST (SGOT)/ INCREASED	62 (50.4)	91 (65.9)	211 (59.3)
BILIRUBIN/ INCREASED	6 (4.9)	9 (6.5)	21 (5.9)
CALCIUM/ DECREASED	16 (13.0)	16 (11.6)	45 (12.6)
CALCIUM/ INCREASED	22 (17.9)	28 (20.3)	63 (17.7)
CPK/ INCREASED	42 (38.5)	55 (50.0)	97 (44.3)
CREATININE/ INCREASED	15 (12.2)	23 (16.7)	58 (16.3)
GLUCOSE/ DECREASED	10 (8.1)	13 (9.4)	38 (10.7)
GLUCOSE/ INCREASED	61 (49.6)	91 (65.9)	203 (57.0)
INR/ INCREASED	17 (13.8)	10 (7.2)	31 (8.7)
LIPASE/ INCREASED	39 (31.7)	69 (50.0)	133 (37.4)
MAGNESIUM/ DECREASED	24 (19.5)	31 (22.5)	71 (19.9)
MAGNESIUM/ INCREASED	7 (5.7)	6 (4.3)	14 (3.9)
PHOSPHOROUS/ DECREASED	37 (30.1)	52 (37.7)	119 (33.4)
POTASSIUM/ DECREASED	18 (14.6)	33 (23.9)	69 (19.4)
POTASSIUM/ INCREASED	14 (11.4)	19 (13.8)	39 (11.0)
SODIUM/ DECREASED	30 (24.4)	31 (22.5)	86 (24.2)
SODIUM/ INCREASED	9 (7.3)	10 (7.2)	23 (6.5)

/bdm/tbos/AP26113/submissions/submission_analyses/2018_ALKNCSLC2L_EU_MAA/pooled/tables/t_14_3_8_9_5 10MAY2018 11:35
(Database Cutoff Date: 101: 2016-05-31, 201: 2017-09-29).
[1] 'All Patients' represents the total Safety Population consistent with table definition.
[2] CPK was only collected in Study AP26113-13-201 so the percentage of CPK/ INCREASED is based on the safety population from that study: 109 in 90 mg QD, 110 in 90 to 180 mg QD, and 219 Total

Safety in special populations

- **Age**

Table 79: **Adverse Events by Age Group (AP26113-13-201)**

Type of Adverse Event	Age < 65	Age 65-74	Age 75-84	Age 85+	Total
Number of Patients	167 (76.3)	43 (19.6)	9 (4.1)	0	219 (100.0)
Any TEAE	167 (100.0)	43 (100.0)	9 (100.0)	0	219 (100.0)
Any Serious TEAE	84 (50.3)	27 (62.8)	5 (55.6)	0	116 (53.0)
Fatal	27 (16.2)	7 (16.3)	2 (22.2)	0	36 (16.4)
Hospitalization/Prolong Existing Hospitalization	76 (45.5)	24 (55.8)	5 (55.6)	0	105 (47.9)
Life Threatening	1 (0.6)	0	1 (11.1)	0	2 (0.9)
Disability/Incapacity	2 (1.2)	0	0	0	2 (0.9)
Other (Medically Significant)	15 (9.0)	3 (7.0)	1 (11.1)	0	19 (8.7)
AE Leading to Drop Out	22 (13.2)	9 (20.9)	0	0	31 (14.2)
Psychiatric Disorders (SOC)	44 (26.3)	11 (25.6)	2 (22.2)	0	57 (26.0)
Nervous System Disorders (SOC)	110 (65.9)	30 (69.8)	8 (88.9)	0	148 (67.6)
Accidents and Injuries (SMQ)	14 (8.4)	7 (16.3)	1 (11.1)	0	22 (10.0)
Cardiac Disorders (SOC)	26 (15.6)	9 (20.9)	0	0	35 (16.0)
Vascular Disorders (SOC)	51 (30.5)	8 (18.6)	4 (44.4)	0	63 (28.8)
Central Nervous System Vascular Disorders (SMQ)	14 (8.4)	2 (4.7)	1 (11.1)	0	17 (7.8)
Infections And Infestations (SOC)	90 (53.9)	22 (51.2)	4 (44.4)	0	116 (53.0)
Anticholinergic Syndrome (SMQ)	79 (47.3)	22 (51.2)	7 (77.8)	0	108 (49.3)
Quality of Life Decreased [1]	0	0	0	0	0
Sum of Postural Hypotension, Falls, Black Outs, Syncope, Dizziness, Ataxia, Fractures [2]	28 (16.8)	15 (34.9)	4 (44.4)	0	47 (21.5)
Other TEAEs Appearing More Frequently in Older Patients [3]					
Decreased Appetite	40 (24.0)	12 (27.9)	5 (55.6)	0	57 (26.0)
Constipation	47 (28.1)	5 (11.6)	2 (22.2)	0	54 (24.7)
Dizziness	21 (12.6)	10 (23.3)	3 (33.3)	0	34 (15.5)
Pyrexia	30 (18.0)	4 (9.3)	0	0	34 (15.5)
Alanine Aminotransferase Increased	29 (17.4)	4 (9.3)	0	0	33 (15.1)
Neck Pain	15 (9.0)	1 (2.3)	0	0	16 (7.3)
Hyperglycaemia	14 (8.4)	0	0	0	14 (6.4)
Memory Impairment	8 (4.8)	2 (4.7)	3 (33.3)	0	13 (5.9)
Vision Blurred	5 (3.0)	5 (11.6)	3 (33.3)	0	13 (5.9)
Dermatitis Acneiform	10 (6.0)	0	0	0	10 (4.6)
Dry Skin	10 (6.0)	0	0	0	10 (4.6)
Malignant Pleural Effusion	6 (3.6)	2 (4.7)	2 (22.2)	0	10 (4.6)

(Database Cutoff Date: 2017-09-29)
Abbreviations: SOC - System Organ Class; SMQ - Standardized MedDRA Query
[1] Defined using Quality of Life Decreased MedDRA Preffered Term
[2] Defined using the following MedDRA Preffered Terms: Postural Hypotension, Orthostatic Hypotension, Fall, Depressed Level of Consciousness, Syncope, Presyncope, Dizziness, Dizziness Postural, Procedural Dizziness, Ataxia, and any Preferred Term that included the word Fracture
[3] TEAEs are summaried by MedDRA Preferred Term. TEAEs were included if the p-value for the Mantel-Haenszel test for linear association with age was less than 0.10 among all patients and the total event frequency was greater than or equal to 10. The MedDRA Preferred Term displayed for specific treatment groups is based on the test among all patients.

- **Hepatic/renal impairment**

No safety data was reported regarding patients with hepatic or renal impairment

Safety related to drug-drug interactions and other interactions

See section 2.5.2 Pharmacokinetics.

Discontinuation due to adverse events

In the safety population, TEAEs that led to discontinuation of brigatinib occurred in a greater proportion of patients in 90/180 mg group than the 90 mg group (11.6% vs 4.1%, respectively).

Table 80: TEAEs Leading to Discontinuation (Safety Population – Studies 101 and 201)

Preferred Term	90 mg QD (N=123)	90 to 180 mg QD (N=138)	Total (N=356)
Number of Patients with at Least One Treatment-Emergent Adverse Event Leading to Treatment Discontinuation	5 (4.1)	16 (11.6)	31 (8.7)
PNEUMONITIS	1 (0.8)	4 (2.9)	6 (1.7)
PNEUMONIA	0 (0.0)	2 (1.4)	3 (0.8)
MYALGIA	0 (0.0)	1 (0.7)	2 (0.6)
NEOPLASM PROGRESSION	0 (0.0)	2 (1.4)	2 (0.6)
PERICARDIAL EFFUSION MALIGNANT	0 (0.0)	2 (1.4)	2 (0.6)
ABDOMINAL PAIN	1 (0.8)	0 (0.0)	1 (0.3)
ACUTE KIDNEY INJURY	0 (0.0)	0 (0.0)	1 (0.3)
AMNESIA	0 (0.0)	0 (0.0)	1 (0.3)
AMYLASE INCREASED	0 (0.0)	0 (0.0)	1 (0.3)
ANGIOEDEMA	0 (0.0)	1 (0.7)	1 (0.3)
DYSPNOEA	0 (0.0)	1 (0.7)	1 (0.3)
GASTRIC ULCER HAEMORRHAGE	0 (0.0)	0 (0.0)	1 (0.3)
GASTROINTESTINAL HAEMORRHAGE	1 (0.8)	0 (0.0)	1 (0.3)
HAEMORRHAGIC STROKE	1 (0.8)	0 (0.0)	1 (0.3)
MALIGNANT PLEURAL EFFUSION	1 (0.8)	0 (0.0)	1 (0.3)
PANCREATITIS	0 (0.0)	1 (0.7)	1 (0.3)
PHOTOSENSITIVITY REACTION	0 (0.0)	1 (0.7)	1 (0.3)
PLEURAL EFFUSION	0 (0.0)	0 (0.0)	1 (0.3)
PULMONARY EMBOLISM	0 (0.0)	0 (0.0)	1 (0.3)
RADIATION PNEUMONITIS	0 (0.0)	1 (0.7)	1 (0.3)
RASH	0 (0.0)	0 (0.0)	1 (0.3)
RESPIRATORY FAILURE	0 (0.0)	1 (0.7)	1 (0.3)
SUICIDAL IDEATION	0 (0.0)	0 (0.0)	1 (0.3)
TACHYCARDIA	0 (0.0)	0 (0.0)	1 (0.3)

(Database Cutoff Date: 101: 2016-05-31, 201: 2017-09-29)

[1] Patients who had an AE action of 'Drug Withdrawn' but whose primary reason for treatment discontinuation was not an adverse event were not included.

[2] Percentages are based on the number of patients recorded. Patients may have more than one AE per preferred term at each level of patient summarization. A patient is counted once for the most severe event.

[3] AEs were classified according to the most recent version of MedDRA available at the time of coding. Certain preferred terms have been regrouped for accuracy.

Safety data from study 301

Safety data have been submitted with data cut 19 February 2018.

The median duration of study drug exposure in patients was longer in the brigatinib arm (9.22 months [range, 0.1-18.4]) compared with the crizotinib arm (7.43 months [range, 0.1-19.2]).

Table 81: Treatment Exposure (Treated Population – study 301)

	Arm A Brigatinib (N = 136)	Arm B Crizotinib (N = 137)
Duration of exposure (months) [a]		
Mean (SD)	8.80 (4.490)	7.66 (4.184)
Median	9.22	7.43
Minimum, maximum	0.1, 18.4	0.1, 19.2
Duration of exposure (n [%])		
<1 month	11 (8.1)	7 (5.1)
1 - <3 months	10 (7.4)	12 (8.8)
3 - <6 months	10 (7.4)	32 (23.4)
6 - <12 months	72 (52.9)	64 (46.7)
≥12 months	33 (24.3)	22 (16.1)
Number of days dosed		
Mean (SD)	266.3 (138.11)	231.3 (131.00)
Median	287.0	225.0
Minimum, maximum	2, 560	4, 603
Total cumulative dose (mg) [b]		

Mean (SD)	43002.6 (23714.10)	111870.8 (65548.94)
Median	44415.0	112000.0
Minimum, maximum	180, 99720	2000, 296000
Dose Intensity (mg/day) [c]		
Mean (SD)	156.26 (35.309)	469.57 (72.480)
Median	173.74	500.00
Minimum, maximum	36.9, 198.0	215.5, 633.3
Relative dose intensity (%) [d]		
Mean (SD)	89.29 (18.139)	92.32 (14.035)
Median	99.59	99.61
Minimum, maximum	24.2, 136.8	43.1, 126.7

Source: Study 301 Table 15.1.9 (data cutoff: 19 February 2018).
[a] Time (months) on study treatment = (last nonzero dose date-first dose date + 1) / 30.4375.
[b] Total cumulative dose does not include doses with "Other Dose Schedule of Administration" equal to "Other."
[c] Total cumulative dose (mg) / time (days) on study treatment.
[d] Total cumulative dose (mg) administered / total dose planned × 100%.

- **Safety Results**

Table 82: Overview of Treatment-Emergent Adverse Events (Treated Population)

	Number of Patients (%)	
	Arm A Brigatinib (N = 136)	Arm B Crizotinib (N = 137)
Patients with TEAEs	132 (97.1)	137 (100.0)
Drug related	116 (85.3)	131 (95.6)
Grade ≥3	83 (61.0)	76 (55.5)
Grade ≥3, drug related	63 (46.3)	39 (28.5)
Leading to study drug discontinuation	16 (11.8)	12 (8.8)
Leading to dose reduction	39 (28.7)	29 (21.2)
Leading to dose interruption	72 (52.9)	58 (42.3)
Patients with SAEs	34 (25.0)	45 (32.8)
Drug related	13 (9.6)	5 (3.6)
Leading to study drug discontinuation	10 (7.4)	6 (4.4)
Deaths within 30 days after last dose or possibly related	7 (5.1)	7 (5.1)

Source: Study 301 Table 15.3.1.1 and 15.3.1.2.6. Data cutoff: 19 February 2018.
Abbreviations: SAE, serious adverse event; TEAE, treatment-emergent adverse event.

- **Treatment-Emergent Adverse Events**

Table 83: TEAEs (in ≥10% in Either Treatment Arm or ≥5% Absolute Difference Between Arms) by Preferred Term (Treated Population)

	Number of Patients (%)	
Preferred Term	**Arm A Brigatinib (N = 136)**	**Arm B Crizotinib (N = 137)**
Patients with any TEAE	132 (97.1)	137 (100.0)
Diarrhoea	67 (49.3)	75 (54.7)
Blood creatine phosphokinase increased	53 (39.0)	21 (15.3)
Nausea	36 (26.5)	77 (56.2)
Cough	34 (25.0)	22 (16.1)
Aspartate aminotransferase increased	31 (22.8)	34 (24.8)
Hypertension	31 (22.8)	10 (7.3)
Alanine aminotransferase increased	26 (19.1)	44 (32.1)
Lipase increased	26 (19.1)	16 (11.7)
Vomiting	25 (18.4)	54 (39.4)
Fatigue	24 (17.6)	28 (20.4)
Dyspnoea	24 (17.6)	25 (18.2)
Constipation	20 (14.7)	57 (41.6)
Headache	20 (14.7)	18 (13.1)
Amylase increased	19 (14.0)	9 (6.6)
Pruritus	18 (13.2)	6 (4.4)
Back pain	17 (12.5)	17 (12.4)
Asthenia	15 (11.0)	22 (16.1)
Pyrexia	15 (11.0)	17 (12.4)
Rash	14 (10.3)	3 (2.2)
Dizziness	13 (9.6)	21 (15.3)
Blood alkaline phosphatase increased	13 (9.6)	17 (12.4)
Abdominal pain	11 (8.1)	17 (12.4)
Decreased appetite	10 (7.4)	27 (19.7)
Arthralgia	10 (7.4)	14 (10.2)
Dermatitis acneiform	9 (6.6)	2 (1.5)
Dyspepsia	8 (5.9)	18 (13.1)
Epistaxis	8 (5.9)	0
Bradycardia	7 (5.1)	17 (12.4)
Blood cholesterol increased	7 (5.1)	0
Hypokalaemia	7 (5.1)	0
Oedema peripheral	6 (4.4)	53 (38.7)
Dysgeusia	6 (4.4)	26 (19.0)
Abdominal pain upper	6 (4.4)	18 (13.1)
Pain in extremity	6 (4.4)	17 (12.4)
Blood creatinine increased	3 (2.2)	19 (13.9)
Neutrophil count decreased	2 (1.5)	12 (8.8)
Pleural effusion	2 (1.5)	9 (6.6)
Photopsia	1 (0.7)	28 (20.4)
Gastrooesophageal reflux disease	1 (0.7)	12 (8.8)
Hypoalbuminaemia	1 (0.7)	8 (5.8)
Visual impairment	0	22 (16.1)
Deep vein thrombosis	0	8 (5.8)

Source: Study 301 Table 15.3.1.2.1.2 (data cutoff: 19 February 2018).
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.
Patients with 1 or more TEAEs within a level of MedDRA term are counted only once in that level.

Table 84: Grade ≥3 TEAEs (in ≥2% of Patients in Either Treatment Arm) by System Organ Class and Preferred Term (Treated Population)

System Organ Class Preferred Term	Number of Patients (%)			
	Arm A Brigatinib (N = 136)		Arm B Crizotinib (N = 137)	
	Any	Grade ≥3	Any	Grade ≥3
Patients with any TEAE	132 (97.1)	83 (61.0)	137 (100)	76 (55.5)
Infections and infestations	50 (36.8)	9 (6.6)	55 (40.1)	10 (7.3)
Pneumonia	8 (5.9)	5 (3.7)	5 (3.6)	4 (2.9)
Urinary tract infection	7 (5.1)	1 (0.7)	10 (7.3)	3 (2.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (5.9)	4 (2.9)	8 (5.8)	5 (3.6)
Neoplasm progression	1 (0.7)	1 (0.7)	3 (2.2)	3 (2.2)
Blood and lymphatic system disorders	8 (5.9)	3 (2.2)	13 (9.5)	5 (3.6)
Neutropenia	0	0	4 (2.9)	3 (2.2)
Metabolism and nutrition disorders	42 (30.9)	7 (5.1)	44 (32.1)	10 (7.3)
Decreased appetite	10 (7.4)	1 (0.7)	27 (19.7)	4 (2.9)
Vascular disorders	36 (26.5)	14 (10.3)	31 (22.6)	5 (3.6)
Hypertension	31 (22.8)	13 (9.6)	10 (7.3)	4 (2.9)
Respiratory, thoracic and mediastinal disorders	77 (56.6)	13 (9.6)	65 (47.4)	10 (7.3)
Dyspnoea	24 (17.6)	3 (2.2)	25 (18.2)	6 (4.4)
Pulmonary embolism	3 (2.2)	3 (2.2)	7 (5.1)	4 (2.9)
Gastrointestinal disorders	96 (70.6)	9 (6.6)	119 (86.9)	19 (13.9)
Diarrhoea	67 (49.3)	2 (1.5)	75 (54.7)	3 (2.2)
Nausea	36 (26.5)	2 (1.5)	77 (56.2)	4 (2.9)
Vomiting	25 (18.4)	1 (0.7)	54 (39.4)	3 (2.2)
General disorders and administration site conditions	68 (50.0)	6 (4.4)	99 (72.3)	9 (6.6)
Non-cardiac chest pain	7 (5.1)	0	11 (8.0)	3 (2.2)
Investigations	86 (63.2)	48 (35.3)	83 (60.6)	34 (24.8)
Blood creatine phosphokinase increased	53 (39.0)	22 (16.2)	21 (15.3)	2 (1.5)
Aspartate aminotransferase increased	31 (22.8)	2 (1.5)	34 (24.8)	8 (5.8)
Alanine aminotransferase increased	26 (19.1)	2 (1.5)	44 (32.1)	13 (9.5)
Lipase increased	26 (19.1)	18 (13.2)	16 (11.7)	7 (5.1)
Amylase increased	19 (14.0)	7 (5.1)	9 (6.6)	1 (0.7)
Blood alkaline phosphatase increased	13 (9.6)	3 (2.2)	17 (12.4)	1 (0.7)
Neutrophil count decreased	2 (1.5)	0	12 (8.8)	6 (4.4)

Source: Study 301 Table 15.3.1.2.1.4 (data cutoff: 19 February 2018).
Abbreviations: incl, including; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.
Patients with 1 or more TEAEs within a level of MedDRA term are counted only once in that level.

- **Serious Adverse Events**

The incidence of serious adverse events (SAE) was similar across the 2 arms (25.0% patients receiving brigatinib and 32.8% patients receiving crizotinib).

SAE in the vascular, psychiatric, respiratory and general disorders SOC disorders were more frequent in patients receiving brigatinib.

SAE in the infestations, eye, ear, gastrointestinal and disorders SOCs were more frequent in Arm B.

SAE in the neoplasm, nervous system, cardiac, musculoskeletal, renal disorders, investigations, injury and uncoded SOCs were similar in both arms, often with an incidence of < 2%.

Table 85: Treatment-Emergent SAEs (in ≥2% of Patients in Either Treatment Arm) by System Organ Class and Preferred Term (Treated Population)

System Organ Class Preferred Term	Number of Patients (%) [Events] Arm A Brigatinib (N = 136)	 Arm B Crizotinib (N = 137)
Patients with ≥1 treatment-emergent SAE	34 (25.0)	45 (32.8)
Infections and infestations	7 (5.1)	14 (10.2)
Pneumonia	5 (3.7) [6]	4 (2.9) [4]
Urinary tract infection	1 (0.7) [1]	3 (2.2) [3]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (2.2)	5 (3.6)
Neoplasm progression	1 (0.7) [1]	3 (2.2) [3]
Respiratory, thoracic and mediastinal disorders	13 (9.6)	11 (8.0)
Dyspnoea	3 (2.2) [3]	5 (3.6) [5]
Pulmonary embolism	3 (2.2) [3]	4 (2.9) [4]
Pleural effusion	1 (0.7) [2]	3 (2.2) [3]
Gastrointestinal disorders	6 (4.4)	9 (6.6)
Diarrhoea	3 (2.2) [3]	1 (0.7) [2]
General disorders and administration site conditions	7 (5.1)	6 (4.4)
Asthenia	3 (2.2) [3]	0
Non-cardiac chest pain	0	3 (2.2) [3]

Source: Study 301 Table 15.3.1.3.1 (data cutoff: 19 February 2018).
Abbreviation: incl, including; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Patients with 1 or more TEAEs within a level of MedDRA term are counted only once in that level.

Deaths

Table 86: AEs Leading to Death Occurring Within 30 Days After Last Dose of Study Drug and Deaths Possibly Related to Study Drug (Treated Population)

System Organ Class Preferred Term	Number of Patients (%) Arm A Brigatinib (N = 136)	 Arm B Crizotinib (N = 137)
Patients with ≥1 TEAE leading to death occurring within 30 days after the last dose or related to study drug	7 (5.1)	7 (5.1)
Infections and infestations	1 (0.7)	1 (0.7)
Pneumonia	1 (0.7)	1 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (2.2)	1 (0.7)
Lung adenocarcinoma	1 (0.7)	0
Malignant pleural effusion	1 (0.7)	0
Neoplasm progression	1 (0.7)	0
Tumour haemorrhage	0	1 (0.7)
Nervous system disorders	1 (0.7)	1 (0.7)
Cerebrovascular accident	1 (0.7)	0
Ischaemic stroke	0	1 (0.7)
Respiratory, thoracic and mediastinal disorders	0	2 (1.5)
Pleural effusion	0	1 (0.7)
Respiratory failure	0	1 (0.7)
General disorders and administration site conditions	2 (1.5)	2 (1.5)
General physical health deterioration	1 (0.7)	2 (1.5)
Multiple organ dysfunction syndrome	1 (0.7)	0

Source: Study 301 Table 15.3.1.2.6 (data cutoff: 19 February 2018).
Abbreviations: AE, adverse event; incl, including; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.
Patients with 1 or more TEAEs within a level of MedDRA term are counted only once in that level.

Other Significant Adverse Events

Treatment-Emergent Adverse Events Leading to Dose Reduction

Dose reductions due to TEAEs were reported in 28.7% of patients in the brigatinib arm and 21.2% of patients in the crizotinib arm. Dose interruptions due to TEAEs were reported in 52.9% of patients in the brigatinib arm and 42.3% of patients in the crizotinib arm.

Overall, 50.7% of patients in the brigatinib arm and 43.8% of patients in the crizotinib arm had at least 1 dose interruption of ≥3 days. The median duration of the longest dose interruption ≥3 days was 8.0 days (range, 3-41) in the brigatinib arm and 11.5 days (range, 3-32) in the crizotinib arm.

TEAEs that led to discontinuation of study drug occurred in similar proportions in the brigatinib and crizotinib arms (11.8% vs 8.8%, respectively)

- Early Onset Pulmonary Events and Later Onset Pneumonitis Events

Events classified as EOPEs were all reported as ILD or pneumonitis in this study and occurred in 4 of the 136 patients (2.9%) in the brigatinib arm and no patients in the crizotinib arm. Two patients experienced pneumonitis, and 2 patients experienced ILD. The onset of these events ranged from Day 3 to Day 8. All 4 patients discontinued brigatinib because of the early onset ILD/pneumonitis. All events resolved or had improved in severity at the time of the last report.

One of the 136 patients (0.7%) in the brigatinib arm and 3 of the 137 patients (2.2%) in the crizotinib arm had later-onset pneumonitis. The event in the brigatinib arm was Grade 1 and resolved after treatment interruption and dose reduction. The patient subsequently experienced a second event of Grade 1 pneumonitis and brigatinib was discontinued. In the crizotinib arm, the later-onset pneumonitis events included 1 Grade 4 event. One patient discontinued crizotinib because of pneumonitis, and 1 patient had study drug interrupted because of the event; the third patient had discontinued crizotinib 2 days before the onset of pneumonitis. All events in the crizotinib arm resolved or had improved in severity at the time of the data cutoff.

One of the 35 patients in the crizotinib arm who crossed over to brigatinib after PD experienced Grade 3 pneumonitis on Day 3 of crossover to brigatinib. Notably, this patient had ground glass opacities on chest computed tomography before starting brigatinib. Brigatinib was discontinued, and the event was ongoing at the time of the last report.

Overall, 3.7% of patients in the brigatinib arm and 2.2% of patients in the crizotinib arm had an event of ILD/pneumonitis.

- Other events

Other events that occurred more frequently with brigatinib than crizotinib included CPK elevation, hypertension, pancreatic enzyme elevation, and pruritus/rash. Eye disorder AEs (including visual impairment), oedema peripheral, GI toxicity (including diarrhoea, nausea, vomiting, constipation, decreased appetite, dyspepsia, dysgeusia, and abdominal pain upper), and ALT increased were seen more frequently with crizotinib than with brigatinib.

2.3.1. Discussion on clinical safety

Study 201 only included patients with advanced ALK+ NSCLC who had received prior crizotinib; 110 patients received at least one dose of the proposed dose of 90/180 mg QD and 109 patients received at least one dose of 90 mg QD. Therefore, study 201 provides the primary basis for the safety evaluation in ALK+ NSCLC previously treated with crizotinib. **Study 101** included 28 patients with ALK+ NSCLC treated at the proposed dose. New safety data from the ongoing phase III **study (301)** was also submitted. Baseline data showed that the study population was older (median 59 years vs 54 years); ECOG status were slightly better (44% at 0 vs 36% at 0); a lower proportion have CNS metastases (29% vs 69%); and a lower proportion had prior chemotherapy (26.5% vs 73.9%). Other baseline characteristics were similar to study 201.

A study population of 138 patients from phase 2 and 136 patients from phase 3 with ALK+ NSCLC have been exposed to brigatinib at the proposed dose of 90 mg QD for 7 days, then 180 mg QD. Of

these, only the phase II patients have been exposed to prior crizotinib and therefore reflect the target population. The median duration of follow-up in study 201 is 17.9 months. These updated data from the 201 study showed that the median duration of exposure was 402.0 days (13.2 months) in the 90 mg group and 522.0 days (17.2 months) in the 90/180 mg group. At the time of the latest data extraction, 26.6% (59/222) of patients were ongoing. In the 301 study, the median duration of exposure with brigatinib was 9.22 months (range 0.1-18.4 months), with 105 patients being exposed for more than 6 months.

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

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

Clinical toxicities shared with other ALK inhibitors include pneumonitis (later onset), CPK elevations, gastrointestinal toxicity, neuropathy, pancreatitis, fatigue, bradycardia, rash, visual disturbances and hepatic effects. Hypertension is not reported for other ALK inhibitors, but appears to be an ADR for brigatinib based on the observed dose response.

In study 201, excluding patients with lung cancer-related reasons for death, there were 12 patient deaths within 30 days of the last dose. In study 101, excluding patients with lung cancer-related reasons for death, there were 10 patient deaths within 30 days of the last dose. Due to the nature of the underlying disease, it is challenging to assign causality for respiratory deaths. However, it appears that brigatinib-related early onset pulmonary events (EOPEs) may have contributed to the deaths of 4 patients, of which the 3 patients from study 101 were on doses ≥ 180 mg QD at the onset of the event (further discussed below).

There were 9 deaths in the pooled clinical trial database during survival follow-up for which the reason is unknown. The Applicant has reported that all deaths occurred > 30 days after last dose of brigatinib and therefore the issue will not be pursued any further.

Severe, life-threatening, and fatal pulmonary adverse reactions, including those with features consistent with ILD/pneumonitis, can occur in patients treated with Alunbrig (see section 4.8).

Most pulmonary adverse reactions were observed within the first 7 days of treatment. Grade 1-2 pulmonary adverse reactions resolved with interruption of treatment or dose modification. Increased age and shorter interval (less than 7 days) between the last dose of crizotinib and the first dose of Alunbrig were independently associated with an increased rate of these pulmonary adverse reactions. These factors should be considered when initiating treatment with Alunbrig. Patients with a history of ILD or drug-induced pneumonitis were excluded from the pivotal trial.

Some patients experienced pneumonitis later in treatment with Alunbrig. Patients should be monitored for new or worsening respiratory symptoms (e.g., dyspnoea, cough, etc.), particularly in the first week of treatment. Evidence of pneumonitis in any patient with worsening respiratory symptoms should be promptly investigated. If pneumonitis is suspected, the dose of Alunbrig should be withheld, and the patient evaluated for other causes of symptoms (e.g., pulmonary embolism, tumour progression, and infectious pneumonia). The dose should be modified accordingly (see sections 4.2, 4.4 and 4.8 of the SmPC).

The Applicant reviewed cases of pulmonary AEs for evidence of brigatinib-related EOPEs or later onset pneumonitis events. There were 14 cases of at least possible EOPE (6.4%) in study 201, all on the 90 mg QD dose. One event was fatal. In study 102, 11 cases (8.0%) were identified, all but one at starting doses > 90 mg QD. There were 4 fatal cases after clarification from the Applicant. The identified cases were characterised by a pneumonitis-like process during the first week of treatment which in most cases responded to dose interruption and steroids. Two thirds of the cases were severe and over half of cases required discontinuation. Five events (2.3%) of later onset pneumonitis were identified in study 201. There were 2.9% (4/136) brigatinib patients in the 301 study with early onset ILD/pneumonitis, of which 3 cases were severe. It is considered reassuring that the rate of EOPE continues to be low and that all events had resolved or improved at the time of submission, and no deaths from EOPE have so far been observed in the phase 3 trial. This is probably due to increased attention and better handling of these early-onset serious events and may reflect the future risk of EOPE better than the phase 1 and 2 results. In fact, 3 patients died from EOPE in phase 1, 1 patient died in phase 2, and so far no patients have died from this in phase 3, demonstrating a learning curve of better handling and consequential diminished seriousness of this potentially fatal adverse event over time. The rate of later-onset pneumonitis was 0.7% for brigatinib vs 2.2% for crizotinib. The Applicant has not yet any more knowledge about the pathogenesis/etiology, but are endorsing an investigator-initiated study, where it will be explored whether peak reduction in DLCO may be a biomarker for EOPE as well as other relevant secondary endpoints such as systemic inflammatory signatures, immunologic phenotype (e.g. HLA-phenotype), clinical, demographic, and molecular characteristics. EOPE is an important safety issue with brigatinib, and it is noted that patients have died following this event. Therefore, the applicant has agreed to put in place a patient alert card in order to minimise the risk of EOPE and initiate a PASS to further investigate the risk of EOPE and to measure the effectiveness of the patient alert card. In addition, pneumonitis is a known adverse drug reaction to TKI's in this class.

Elevations of hepatic enzymes (aspartate aminotransferase, alanine aminotransferase) and bilirubin have occurred in patients treated with Alunbrig (see section 4.8). Liver function, including AST, ALT and total bilirubin should be assessed prior to the initiation of Alunbrig and then every 2 weeks during the first 3 months of treatment. Thereafter, monitoring should be performed periodically. Based on the severity of the laboratory abnormalities, treatment should be withheld, and the dose modified accordingly (see sections 4.2 and 4.4 of the SmPC).

Elevations of CPK have occurred in patients treated with Alunbrig. Patients should be advised to report any unexplained muscle pain, tenderness, or weakness. CPK levels should be monitored regularly during Alunbrig treatment. Based on the severity of the CPK elevation, treatment with Alunbrig should be withheld, and the dose modified accordingly (see sections 4.2, 4.4 and 4.8 of the SmPC).

Elevations of amylase and lipase have occurred in patients treated with Alunbrig. Lipase and amylase should be monitored regularly during treatment with Alunbrig. Based on the severity of the laboratory abnormalities, treatment with Alunbrig should be withheld, and the dose modified accordingly (see sections 4.2, 4.4 and 4.8 of the SmPC).

Peripheral neuropathy has occurred in patients treated with Alunbrig. Peripheral neuropathy can cause functional impairment and affect quality of life. Peripheral neuropathy is listed as a very common ADR in section 4.8 of the SmPC.

Hypertension has occurred in patients treated with Alunbrig. Blood pressure should be monitored regularly during treatment with Alunbrig. Hypertension should be treated according to standard guidelines to control blood pressure. Heart rate should be monitored more frequently in patients if concomitant use of a medicinal product known to cause bradycardia cannot be avoided. For severe hypertension (≥ Grade 3), Alunbrig should be withheld until hypertension has recovered to Grade 1 or to baseline. The dose should be modified accordingly (see sections 4.2, 4.4 and 4.8 of the SmPC).

Bradycardia has occurred in patients treated with Alunbrig. Caution should be exercised when administering Alunbrig in combination with other agents known to cause bradycardia. Heart rate and blood pressure should be monitored regularly. If symptomatic bradycardia occurs, treatment with Alunbrig should be withheld and concomitant medicinal products known to cause bradycardia should be evaluated. Upon recovery, the dose should be modified accordingly. In case of life-threatening bradycardia, if no contributing concomitant medication is identified or in case of recurrence, treatment with Alunbrig should be discontinued (see sections 4.2, 4.4 and 4.8 of the SmPC).

Visual disturbance adverse reactions have occurred in patients treated with Alunbrig. Patients should be advised to report any visual symptoms. For new or worsening severe visual symptoms, an ophthalmologic evaluation and dose reduction should be considered (see sections 4.2, 4.4 and 4.8 of the SmPC). Retinal degeneration was included as an important potential risk in the RMP (see section 2.4).

In study 201, 69% of patients experienced hyperglycaemia. No patients had dose reductions due to hyperglycaemia. Grade 3 hyperglycemia occurred in 7.3% of patients. Fasting serum glucose should be assessed prior to initiation of brigatinib and monitored periodically thereafter. Antihyperglycaemic treatment should be initiated or optimised as needed. If adequate hyperglycaemic control cannot be achieved with optimal medical management, brigatinib should be withheld until adequate hyperglycaemic control is achieved; upon recovery reducing the dose may be considered or brigatinib may be permanently discontinued (see sections 4.2 and 4.4 of the SmPC).

Dose **interruptions, reductions and discontinuations** due to AEs were reported in 54.5%, 29.1% and 7.3% of the 90/180 mg group, respectively. The proportions were reduced for the 90 mg group. The PTs most commonly involved were pneumonitis, pneumonia and blood CPK increased. Dose reductions and discontinuations of brigatinib in the 301 study were 28.7% and 11.8%, respectively.

Study AP26113-13-301 **(301)** is an ongoing, phase 3, randomized, multicentre study to evaluate the efficacy and safety of brigatinib in patients with advanced ALK+ NSCLC who have not previously received ALK-directed therapy. As mentioned, the exposure is considered short in the phase 3 study, and this may cause an overly optimistic assessment of the safety profile of brigatinib. However, more than grade 3 TEAEs of any causality were greater with brigatinib (61.0% vs 55.5%) and some of the most important adverse events occur early on, such as early-onset pneumonitis (EOPE). A lower fraction had SAEs with brigatinib (25% vs 32.8%), but there were a greater need for dose reduction (28.7% vs 21.2%) and study drug discontinuation (11.8% vs 8.8%) with brigatinib treatment. It is also noted that significantly more patients had CPK increase (39% vs 15.3%), hypertension (22.8% vs 7.3%), and amylase increased (14 vs 6.6%) with brigatinib. Conversely, more patients had nausea (56.2% vs 26.5%) and other GI related symptoms such as constipation, vomiting, and decreased appetite with crizotinib. Hence, brigatinib is associated with reduced GI toxicity and peripheral oedema compared to crizotinib. However, brigatinib is particularly associated with hypertension, as well as creatine phosphokinase, lipase and amylase elevations, confirming these as ADRs. The incidences of AEs by PT were consistent with the 31 May 2016 cut-off of study 201, when brigatinib median exposure was 10.6 months (similar exposure to current study 301 data).

SAEs leading to death were rarely occurring in more than 2% of the patients in each arm and the data are apparently consistent with the phase 2 safety data, although the incidence was lower compared to study 201, as might be expected for an earlier line setting. Additionally, most of the serious adverse events are deemed complications to the underlying cancer disease and not to the given treatments. No new signals were apparent on review of deaths, SAEs and discontinuations due to AE.

Women of childbearing age being treated with Alunbrig should be advised not to become pregnant and men being treated with Alunbrig should be advised not to father a child during treatment. Women of reproductive potential should be advised to use effective non-hormonal contraception during treatment

with Alunbrig and for at least 4 months following the final dose. Men with female partners of reproductive potential should be advised to use effective contraception during treatment and for at least 3 months after the last dose of Alunbrig.

Alunbrig may cause foetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity (see section 5.3). There are no clinical data on the use of Alunbrig in pregnant women. Alunbrig should not be used during pregnancy unless the clinical condition of the mother requires treatment. If Alunbrig is used during pregnancy, or if the patient becomes pregnant while taking this medicinal product, the patient should be apprised of the potential hazard to a foetus.

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

No human data on the effect of Alunbrig on fertility are available. Based on repeat-dose toxicity studies in male animals, Alunbrig may cause reduced fertility in males (see section 5.3). The clinical relevance of these findings to human fertility is unknown (see also non-clinical aspects).

2.3.2. Conclusions on the clinical safety

The safety profile of brigatinib is as expected for ALK inhibitors with the exception of pulmonary adverse reactions. Brigatinib is frequently associated with gastrointestinal effects, cough, blood CPK increased, headache, fatigue, dyspnoea and hypertension. Most toxicities appear manageable, although gastrointestinal effects, fatigue and neuropathy are likely to affect quality of life. The discontinuation rate is only 6.4% and considered relatively low in this heavily pre-treated patient population.

The CHMP considers the following measures necessary to address issues related to safety:

PAES: In order to further characterise the efficacy and safety of brigatinib in the treatment of patients with ALK-positive NSCLC, the MAH should submit the clinical study report of the phase III study AP26113-13-301 comparing brigatinib versus crizotinib in patients with advanced ALK+ NSCLC who have not previously received ALK-directed therapy.

2.4. Risk Management Plan

Safety concerns

Summary of Safety Concerns	
Important identified risks	• Pulmonary toxicity (including EOPEs and later-onset pneumonitis). • Hypertension. • Bradycardia. • DDI with strong CYP3A inhibitors and strong and moderate CYP3A inducers.
Important potential risks	• Hepatotoxicity. • Myopathy, including rhabdomyolysis and cardiomyopathy. • Pancreatitis. • Retinal degeneration, macular degeneration. • Embryofetal and developmental toxicity.
Missing information	• Effects on male and/or female fertility. • Long-term safety. • DDI with CYP3A4 substrates.

Abbreviations: CYP, cytochrome P-450; DDI, drug-drug interaction; EOPE, early-onset pulmonary

event.

Pharmacovigilance plan

Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the MA				
None	Not applicable	Not applicable	Not applicable	Not applicable
Category 2 – Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional MA or a MA under exceptional circumstances				
None	Not applicable	Not applicable	Not applicable	Not applicable
Category 3 - Required additional pharmacovigilance activities				
EU PASS, Planned	To describe the occurrence and outcome of EOPE in ALK+ NSCLC patients on brigatinib therapy or other TKIs. To assess patient receipt and use of the brigatinib PAC.	Pulmonary toxicity (including EOPEs and later-onset pneumonitis)	Protocol submission Final report	28 Feb 2019 31 Dec 2024

Abbreviations: ALK+, anaplastic lymphoma kinase positive; EOPE, early-onset pulmonary event(s); EU, European Union; MA, marketing authorization; NSCLC, non–small-cell lung cancer; PAC, patient alert card; PASS, postapproval safety study; Q, quarter.

Risk minimisation measures

Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Pulmonary toxicity (including EOPEs and later-onset pneumonitis) (important identified risk)	**Routine risk minimization measures:** SmPC Sections: 4.2 Posology and method of administration (ILD/pneumonitis) 4.4 Special warnings and precautions for use (pulmonary adverse reactions) 4.8 Undesirable effects (pulmonary adverse reactions) **Additional risk minimization measures:** Patient alert card	**Additional pharmacovigilance activities:** Brigatinib PASS
Hypertension (important identified risk)	**Routine risk minimization measures:** SmPC Sections: 4.2 Posology and method of	**Additional pharmacovigilance activities:** None

Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	administration 4.4 Special warnings and precautions for use 4.8 Undesirable effects	
Bradycardia (important identified risk)	**Routine risk minimization measures:** SmPC Sections: 4.2 Posology and method of administration 4.4 Special warnings and precautions for use 4.8 Undesirable effects	**Additional pharmacovigilance activities:** None
DDI with strong CYP3A inhibitors and strong and moderate CYP3A inducers (important identified risk)	**Routine risk minimization measures:** SmPC Sections: 4.4 Special warnings and precautions for use (DDIs) 4.5 Interaction with other medicinal products and other forms of interaction (CYP3A inhibitors; CYP3A inducers)	**Additional pharmacovigilance activities:** None
Hepatotoxicity (important potential risk)	**Routine risk minimization measures:** SmPC Sections: 4.2 Posology and method of administration (elevation of hepatic enzymes) 4.4 Special warnings and precautions for use (elevations of hepatic enzymes) 4.8 Undesirable effects (elevation of hepatic enzymes)	**Additional pharmacovigilance activities:** None
Myopathy, including rhabdomyolysis and cardiomyopathy (important potential risk)	**Routine risk minimization measures:** SmPC Sections: 4.2 Posology and method of administration 4.4 Special warnings and precautions for use (CPK elevation) 4.8 Undesirable effects	**Additional pharmacovigilance activities:** None
Pancreatitis (important potential risk)	**Routine risk minimization measures:** SmPC Sections: 4.2 Posology and method of administration (elevation of lipase or amylase) 4.4 Special warnings and precautions for use (elevations of pancreatic enzymes) 4.8 Undesirable effects (elevations of pancreatic enzymes)	**Additional pharmacovigilance activities:** None

Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Retinal degeneration, macular degeneration (important potential risk)	**Routine risk minimization measures:** SmPC Sections: 4.2 Posology and method of administration (visual disturbance) 4.4 Special warnings and precautions for use (visual disturbance) 4.8 Undesirable effects (visual disturbance)	**Additional pharmacovigilance activities:** None
Embryofetal and developmental toxicity (important potential risk)	**Routine risk minimization measures:** SmPC Sections: 4.6 Fertility, pregnancy and lactation 5.3 Preclinical safety data	**Additional pharmacovigilance activities:** None
Effects on male and/or female fertility (missing information)	**Routine risk minimization measures:** SmPC Sections: 4.6 Fertility, pregnancy and lactation 5.3 Preclinical safety data	**Additional pharmacovigilance activities:** None
Long-term safety (missing information)	**No risk minimization measures**	**Additional pharmacovigilance activities:** None
DDI with CYP3A4 substrates (missing information)	**Routine risk minimization measures:** SmPC Section: 4.5 Interaction with other medicinal products and other forms of interaction	**Additional pharmacovigilance activities:** None

Abbreviations: CPK, creatine phosphokinase; CYP, cytochrome P-450; DDI, drug-drug interaction; EOPE, early-onset pulmonary event(s); ILD, interstitial lung disease; PAC, patient alert card; PASS, postapproval safety study; SmPC, Summary of Product Characteristics.

Conclusion

The CHMP and PRAC considered that the risk management plan version 5.0 is acceptable.

2.5. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR

cycle with the international birth date (IBD). The IBD is 28 April 2017. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.6. New Active Substance

The applicant compared the structure of brigatinib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers brigatinib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.7. Product information

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Alunbrig (brigatinib) is included in the additional monitoring list as it contains a new active substance.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication is as monotherapy for adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) who were previously treated with crizotinib.

3.1.2. Available therapies and unmet medical need

ALK inhibitors are currently the main treatment options, and crizotinib was approved for first-line treatment at the time of application. Since then, alectinib and ceritinib have gained approval in the first-line setting and in the second line post-crizotinib.

3.1.3. Main clinical studies

Data from two early studies are provided, a phase 1 study AP26113-11-101, the pivotal phase 2 study AP26113-13-201, supported by top-line results from the ongoing phase 3 study AP26113-13-301. The phase 1 and 2 studies were both open-label studies, non-randomised, single arm studies with no comparator as the phase 2 study randomised patients for two dosing regimens and was not designed for comparison regarding differences in efficacy.

3.2. Favourable effects

The 90/180 mg cohort of **study 101** included 25 patients with ALK+ NSCLC previously treated with crizotinib, and therefore of relevance for this application. In this group, 76.0% (95% CI: 54.9%, 90.6%) had a confirmed objective response. The KM estimate median duration of response for the 90/180 mg dose group was 26.1 months (95% CI: 7.9, 26.1). The KM estimate of median PFS for patients in the 90 mg/180 mg QD group was 16.3 months (95% CI: 9.2, not reached). Median overall survival (KM estimate) was not reached in this group.

Of those with ALK+ NSCLC previously treated with crizotinib in the 90/180 mg QD group of study 101, there were 18 evaluable patients with brain metastases at baseline, of which 8 (44.4%; 95% CI: 21.5%, 69.2%) had a confirmed response by IRC. The KM estimate median intracranial duration of response was 11.4 months (95% CI: 5.6, 11.4).

In **study 201**, a total of 222 patients were randomised to brigatinib 90 mg (n=112) or brigatinib 90/180 mg (n=110). For the primary outcome of confirmed ORR by investigator assessment in the ITT population, the rate was 55.5% (97.5% CI: 44.3, 66.2) for the 90/180 mg group. The KM estimate median investigator-assessed duration of response was 13.8 months (95% CI: 10.2, 17.5) for patients in 90/180 mg group. The KM estimate median PFS was 15.6 months (95% CI: 11.1, 19.4) for the 90 mg/180 mg group. The median OS was 27.6 months (95% CI: 27.6; not reached) in the 90/180 mg group.

Brigatinib showed promising efficacy in the CNS, especially regarding the intracranial PFS of 18.4 months for patients with any brain metastases at baseline (n=73, measurable and non-measurable only). In patients with measurable brain metastases at baseline, the intracranial ORR by IRC was 66.7% i.e. 12/18 patients (95% CI: 41.0, 86.7) at the 90/180 mg dose level. The median duration of intracranial response was 16.6 months, and over half of responders maintained response for at least 12 months.

3.3. Uncertainties and limitations about favourable effects

Although study 201 was randomised, the design was open-label and no placebo or active comparator arm has been included. Thus, the effect on time-related endpoints like OS and PFS is unknown. In order to further confirm the efficacy and safety of brigatinib in the treatment of patients with ALK-positive NSCLC, the MAH should submit the clinical study report of the phase III study AP26113-13-301 comparing brigatinib versus crizotinib in patients with advanced ALK+ NSCLC who have not previously received ALK-directed therapy.

The study population was not a reflection of the patient population regarding performance status, as only a few patients (8.2% in the high dose group) were PS 2 and the rest PS 0-1, and this may lead to selection bias.

3.4. Unfavourable effects

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

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

Clinical toxicities shared with other ALK inhibitors include pneumonitis (later onset), CPK elevations, gastrointestinal toxicity, neuropathy, pancreatitis, fatigue, bradycardia, rash, visual disturbances and hepatic effects. Hypertension is not reported for other ALK inhibitors, but appears to be an adverse drug reaction (ADR) for brigatinib based on the observed dose response.

Brigatinib is associated with early onset pulmonary events (EOPEs), characterised by a pneumonitis-like process during the first week of treatment. There were 14 cases of definite or possible EOPEs (6.4%) in study 201, all on the 90 mg QD dose at the time of onset. One event was fatal. In study 102, 11 cases (8.0%) were identified, all but one at starting doses > 90 mg QD. There were 4 fatal cases. Two thirds of the EOPE cases were severe and over half of cases required discontinuation. Five events (2.3%) of later onset pneumonitis were identified in study 201.

Peripheral neuropathy was reported by 28% of patients treated with 90/180 mg regimen in studies 101 and 201. In patients who reported peripheral neuropathy AEs (Peripheral Sensory Neuropathy and Paraesthesia) in the 90/180 mg group of study 201, the event lasted more than 6 months in half of the cases. In more than half of patients, there was no resolution of any peripheral neuropathy events.

During the procedure, the Applicant submitted safety data from the ongoing 301 study, and the results did not alter the safety profile of brigatinib. Especially, no new fatal cases of EOPE were observed, indicating that this event may be more manageable than anticipated.

3.5. Uncertainties and limitations about unfavourable effects

It is still not known whether any biomarkers such as HLA allelic variants are associated with brigatinib-related EOPEs. However, the Applicant are endorsing an investigator-initiated study, where it will be explored whether peak reduction in DLCO may be a biomarker for EOPE as well as other relevant secondary endpoints such as systemic inflammatory signatures, immunologic phenotype (e.g. HLA-phenotype), clinical, demographic, and molecular characteristics. In addition, the Applicant has agreed to put in place a patient alert card in order to minimise the risk of EOPE and initiate a **PASS** to further investigate the risk of EOPE and to measure the effectiveness of the patient alert card.

3.6. Effects Table

Table 87: Effects Table for Alunbrig 180mg QD in ALK positive NSCLC after crizotinib (data cut-off: 29 September 2017)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
ORR	Proportion of patients with a confirmed CR or PR on subsequent tumour assessment	% (95% CI)	56.4 (45.2, 67.0)	N/A	Data from 110 patients in the pivotal trial as efficacy data was not pooled with data from phase 1 who got 180mg QD (n=28)	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
DOR	Duration of response in patients with a RECIST Version 1.1 CR or PR as determined by investigator assessment	Months (95% CI)	13.8 (10.2, 19.3)	N/A		
PFS	Time from date of first dose to date of disease progression or death	Median, months (95% CI)	15.6 (11.1, 21.0)	N/A		
Unfavourable Effects: All patients population (n=219)						
Serious TEAE		%	53.0	N/A		
Grade ≥ 3 TEAE		%	67.1	N/A		
TEAE with an outcome of death		%	14.6	N/A		
Lymphocyte count decreased ADR (G3/4)		%	20	N/A		
Lipase increased ADR (G3/4)		%	12	N/A		
Hypertension ADR (G3/4)		%	10	N/A		
Amylase increased ADR (G3/4)		%	9	N/A		
Hyperglycaemia ADR (G3/4)		%	6	N/A		
Pneumonitis ADR (G3/4)		%	4	N/A	Class effect	

Abbreviations: TAE: Treatment Emergent Event. CPK: Creatine Phosphokinase. QD: Once a day. EOPE: Early Onset Pulmonary Events.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The ORR and the KM duration of response support the efficacy of Brigatinib in ALK+ NSCLC patients previously treated with crizotinib. Updated phase 2 results are consistent with previously submitted data both regarding safety and efficacy and the submitted phase 3 top-line results further support the efficacy of brigatinib.

An effect on brain metastases is particularly relevant in this patient population as half of them have brain metastases at progression.

The unfavourable effect of most concern is a 6% incidence of early onset pulmonary events characterised by a pneumonitis-like process during the first week of treatment. Two thirds of the cases were severe and over half of cases required discontinuation. Four fatal cases were reported, 3 patients in phase 1 and 1 patient in phase 2. An incidence of EOPE of 2.9% was reported in the 301 study, however, all events had resolved or improved at the time of submission, and so no deaths from EOPE have so far been observed in the phase 3 trial. This is probably due to increased attention to these early onset serious events and may reflect the future risk of EOPE. This effect appears to be unique to brigatinib, among ALK inhibitors, but with appropriate precautions, it should be acceptable in this palliative treatment setting.

Gastrointestinal toxicity appears to be manageable, with a low frequency of severe events, however, even low grade events may affect quality of life. Other common toxicities that are likely to affect quality of life include fatigue and peripheral neuropathy. The 10% discontinuation rate mainly reflected pulmonary AEs, suggesting that overall, the other toxicities were manageable, having in mind that the study population was heavily pre-treated, with a less than optimal performance status.

3.7.2. Balance of benefits and risks

The benefit of brigatinib following failure on crizotinib is considered clinically relevant. Additionally, the safety profile of brigatinib is acceptable. Therefore, the benefit risk balance is positive.

3.7.3. Additional considerations on the benefit-risk balance

3.8. Conclusions

The overall B/R of Alunbrig is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Alunbrig is favourable in 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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch of Alunbrig in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where Alunbrig is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use Alunbrig have access to/are provided with the following educational package:

A patient alert card

- **The patient alert card** shall contain the following key messages:
  - A warning message for health care professionals treating the patient at any time, including in conditions of emergency, that the patient is using Alunbrig
  - That Alunbrig treatment may increase the risk of early onset pulmonary events (including interstitial lung disease and pneumonitis)
  - Signs or symptoms of the safety concern and when to seek attention from a HCP
  - Contact details of the Alunbrig prescriber

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the following measure:

Description	Due date
Post-authorisation efficacy study (PAES): In order to further characterise the efficacy and safety of brigatinib in the treatment of patients with ALK-positive NSCLC, the MAH should submit the clinical study report of the phase III study AP26113-13-301 comparing brigatinib versus crizotinib in patients with advanced ALK+ NSCLC who have not previously received ALK-directed therapy.	31 December 2020

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that brigatinib is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.