CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208772Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multidisciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	208772
Priority or Standard	Priority
Submit Date(s)	August 29, 2016
Received Date(s)	August 29, 2016
PDUFA Goal Date	April 29, 2017
Division/Office	DOP2/OHOP
Review Completion Date	April 28, 2017
Established Name	Brigatinib
(Proposed) Trade Name	ALUNBRIG
Pharmacologic Class	Kinase inhibitor
Code name	AP26113
Applicant	ARIAD Pharmaceuticals, Inc.
Formulation(s)	Tablet
Dosing Regimen	90 mg orally once daily for the first seven days, then, if tolerated, 180 mg orally once daily
Applicant Proposed Indication(s)/Population(s)	ALUNBRIG™ is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.
Recommendation on Regulatory Action	Accelerated approval
Recommended Indication(s)/Population(s) (if applicable)	ALUNBRIG is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management
DMPP = Division of Medical Policy Programs
QT-IRT = QT Interdisciplinary Review Team

Glossary

AC	Advisory Committee
ACLS	Advanced Cardiac Life Support
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALK	anaplastic lymphoma kinase
BIRC	blinded independent central review committee
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CT	Computed Tomography
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
DoR	duration of response
ECG	electrocardiogram
eCTD	electronic common technical document
EGFR	epidermal growth factor receptor
EML4	echinoderm microtubule-associated protein-like 4
EOPE	early onset pulmonary event
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HR	hazard ratio

ICH	International Conference on Harmonization
IND	Investigational New Drug
IRC	independent central review
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NE	not estimable
NME	new molecular entity
NSCLC	non-small cell lung cancer
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	objective response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PD-1	programmed death-1
PFS	progression-free survival
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	Preferred Term
RECIST	Response Evaluation Criteria In Solid Tumors
REMS	risk evaluation and mitigation strategy
RP2D	recommended Phase II dose
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
U.S.	United States

USPI US Prescribing Information

APPEARS THIS WAY ON ORIGINAL

1 Executive Summary

1.1. Product Introduction

ARIAD Pharmaceuticals, Inc. (ARIAD) submitted NDA 208772 for brigatinib (ALUNBRIG), a new molecular entity, for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. Brigatinib is a tyrosine kinase inhibitor with in vitro activity against multiple kinases including ALK, ROS1, and IGF-1. The proposed dosing regimen is 90 mg orally once daily for seven days followed by (if tolerated) 180 mg orally once daily until disease progression or unacceptable toxicity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommendation for accelerated approval according to 21 CFR 314.510 Subpart H is primarily based on the results of a single trial (ALTA) that demonstrated a durable 53% Independent Review Committee-assessed response rate in 110 patients in the study arm where patients received the brigatinib dose proposed in product labeling. A similar effect was observed when study radiographs were assessed by the investigators and responses were also observed when patients received a lower dose of brigatinib. FDA has accepted response rate as an approval endpoint for non-small cell lung cancer because such responses would not occur by chance alone (in general, in the absence of therapy, tumors grow or remain stable rather than shrinking). Anti-tumor responses were observed in this international study across study sites and across various subgroups. OSI found that the primary efficacy endpoint, objective response rate (ORR) to be verifiable at four inspected clinical sites. Investigator-assessed responses rates above 50% were also found in two arms in a smaller supportive clinical study, increasing confidence in the findings of the pivotal ALTA trial. Based on these findings, I expect that brigatinib will have (as described in section 505(d) of the Act) “the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.”

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Brigatinib (ALUNBRIG) is a tyrosine kinase inhibitor with in vitro activity against multiple kinases including ALK, ROS1, and IGF-1. Brigatinib is intended for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. I recommend approval of brigatinib based on submitted data demonstrating a favorable risk-benefit profile.

Metastatic ALK-positive lung cancer is a fatal, incurable disease. Crizotinib is an approved ALK-inhibitor for patients with ALK-positive NSCLC; however most patients progress on crizotinib within a year (shorter for conventional chemotherapy). Ceritinib and alectinib are approved for patients with ALK-positive NSCLC after progression on crizotinib. Both drugs are approved under FDA's Accelerated Approval program for the treatment of ALK-positive NSCLC, and therefore are not considered available therapy because "FDA recognizes, as a general matter, that it is preferable to have more than one treatment approved under the accelerated approval provisions because of the possibility that clinical benefit may not be verified in post-approval confirmatory trials." An unmet need exists for patients with ALK-1-positive NSCLC because responses to cytotoxic chemotherapy are generally of short duration and cytotoxic chemotherapy is associated with substantial toxicity.

Approximately half of the 222 patients enrolled in the trial supporting the approval of brigatinib experienced an objective response (tumor shrinkage of at least 30% in measured lesions) after receiving brigatinib. Median duration of response was approximately 14 months indicating that responses were durable. Central nervous system (CNS) metastases also responded to treatment with brigatinib. These systemic and CNS responses represent an important effect that is expected to translate into tangible clinical benefits in patients with ALK-positive NSCLC, especially considering that patients would ordinarily receive cytotoxic chemotherapy and that the malignancy is a fatal disease.

Most of the adverse reactions caused by brigatinib appear manageable with supportive care or dose modification. These include risks described in the Warnings and Precautions section of labeling including hypertension (high blood pressure), bradycardia (slow heart rate), creatine phosphokinase (CPK) elevation, pancreatic enzyme elevation, and hyperglycemia (elevated glucose levels).

Other important but less common adverse reactions include severe pulmonary toxicity such as pneumonitis, which can occur early during treatment, and visual toxicity. Pancreatitis and rhabdomyolysis (a severe/serious condition in which muscle fibers break down, potentially leading to kidney failure) may need to be followed in the post-marketing setting based on the observed laboratory findings. CPK elevation was the most common adverse reaction leading to dose reduction of brigatinib in the ALTA study. A limitation of the database was lack of a non-brigatinib comparator arm. ARIAD will obtain additional data regarding risk in an ongoing randomized study comparing brigatinib to crizotinib in the first-line setting. Additional uncertainties regarding risk in special populations will be addressed in post-marketing commitments or requirements. Specifically ARIAD will conduct trials to assess the safety and pharmacokinetics of brigatinib in patients with moderate to severe liver impairment, severe kidney impairment, and in patients who are receiving drugs that affect a liver enzyme called CYP3A4 (this enzyme that can metabolize (break down) certain drugs).

Risks will primarily be communicated in product labeling and patient labeling. Although brigatinib can cause severe/serious toxicities, brigatinib will be prescribed by oncologists who by training understand how to monitor, identify, and manage such toxicities. Such an approach is standard in the practice of medical oncology.

In summary, I conclude that brigatinib has a favorable risk-benefit profile for the intended population based on the high (durable) response rate observed in a patient population with high unmet medical need. This effect was large in magnitude when compared to historical effects of cytotoxic chemotherapy and will be important for patients with metastatic ALK-positive NSCLC who would otherwise die without additional therapy. Although brigatinib can cause severe/serious toxicities, such risks and uncertainties regarding the risks are considered acceptable given the durable responses observed in a patient population with progressive life-threatening NSCLC.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Metastatic ALK-positive non-small cell lung cancer (NSCLC) is a serious and life threatening disease. Lung cancer can cause life-altering symptoms including cough, fatigue, pain, weight loss, and shortness of breath. Lung cancer can also increase the risk of infections. • Tumors from approximately 3-7% of patients with NSCLC have a rearrangement (a specific abnormality) in the anaplastic lymphoma kinase	Metastatic ALK-positive lung cancer is a fatal, incurable disease. Although crizotinib is an approved ALK-inhibitor, most patients progress on crizotinib within a year (shorter for conventional chemotherapy). Additional therapies

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(ALK) gene. ALK-rearrangements have been reported to occur more frequently in younger patients and in light or never smokers. • Prior to the approval of second generation drugs to treat patients with ALK-positive lung cancer, most patients would die within two years of treatment with crizotinib (approved first generation ALK inhibitor) or standard cytotoxic chemotherapy. • Brain metastases have been reported to occur in about 1 in 5 patients without brain metastases at baseline who receive crizotinib.	are needed for these patients.
Current Treatment Options	• Crizotinib, an ALK-inhibitor, received regular FDA approval for the treatment of patients with metastatic ALK-positive NSCLC and has a favorable risk-benefit profile when compared against standard cytotoxic chemotherapy. • Resistance occurs during crizotinib treatment and therefore patients progress on crizotinib. • FDA approved two other ALK-inhibitors, ceritinib and alectinib, for the treatment of ALK-positive NSCLC after progression on crizotinib under the Accelerated Approval program. FDA approved both drugs based on the demonstration of objective durable responses (i.e., tumor shrinkage). • Other therapeutic options include cytotoxic chemotherapy or immunotherapy. • Immunotherapy drugs (either pembrolizumab or nivolumab) are approved for patients with ALK rearrangements *after* disease progression on FDA-approved therapy for these rearrangements. Uncertainty exists regarding effects of immunotherapy drugs in patients with ALK-rearrangements; however, literature reports (e.g., Gainor JF et al., 2016) indicate that response rates may be lower in patients with ALK- or EGFR-aberrations. • Responses to cytotoxic chemotherapy are generally of short duration and cytotoxic chemotherapy is associated with substantial toxicity (for example, hematologic and gastrointestinal toxicity).	Although ceritinib and alectinib are approved under FDA's Accelerated Approval program, as discussed in FDA Guidance, "FDA recognizes, as a general matter, that it is preferable to have more than one treatment approved under the accelerated approval provisions because of the possibility that clinical benefit may not be verified in post-approval confirmatory trials." Therefore, brigatinib addresses an unmet medical need.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The benefits of brigatinib were determined in a randomized clinical trial that enrolled 222 patients with locally advanced or metastatic ALK-positive NSCLC who progressed on prior treatment with crizotinib. • Approximately half of the patients experienced an objective response (tumor shrinkage of at least 30% in measured lesions) after receiving brigatinib. Median duration of response was approximately 14 months. • Approximately two-thirds of 18 patients with measurable brain metastases at baseline who received the proposed 90→180 mg dosing regimen experienced a CNS response. Based on the limited duration of follow-up, ARIAD has agreed to provide additional data post-marketing regarding the duration of response in these patients. • This effect on tumor shrinkage (and on shrinkage of tumors metastatic to the brain) is reasonably likely to predict clinical benefit. Uncertainty regarding the clinical effects of brigatinib will be further assessed in an ongoing clinical trial against crizotinib in the first-line setting. Nevertheless, because of the clinically meaningful anti-tumor effects observed to date, availability of other ALK-inhibitors including alectinib and ceritinib, and other available therapies (e.g., chemotherapy or immunotherapy), equipoise does not exist to conduct a placebo controlled trial to isolate effects on PFS or OS with certainty.	The submitted data in this NDA meets the statutory standards for accelerated approval. The observed response rates (and duration of response) appear clinically meaningful and provides for a meaningful advantage over available therapy. Brigatinib induces an objective response per RECIST in about half of patients and appears to be able to shrink CNS tumors.
Risk	• Risk was primarily assessed in a single trial (ALTA) that evaluated 219 patients with locally advanced or metastatic ALK-positive NSCLC who received one of two dosing regimens of brigatinib. In ALTA, 110 patients were randomly allocated to receive the dose described in product labeling: 90 mg daily for seven days followed by 180 mg daily. • The limited size of the safety database precluded substantive conclusions regarding safety in subgroups (for example, by age, race, or gender). • Most of the adverse reactions caused by brigatinib appear manageable with supportive care or dose modification. These include risks described in the Warnings and Precautions section of labeling including hypertension (high blood pressure), bradycardia (slow heart rate), creatine	Although brigatinib can cause severe/serious toxicities, such risks and uncertainties regarding the risks are considered acceptable given the durable responses observed in a patient population with progressive life-threatening NSCLC. In general, brigatinib appears to have a reasonable safety profile and most toxicities related to brigatinib appear manageable with supportive care or

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	phosphokinase (CPK) elevation, pancreatic enzyme elevation, and hyperglycemia (elevated glucose levels). Pancreatitis and rhabdomyolysis (a severe/serious condition in which muscle fibers break down, potentially leading to kidney failure) may need to be followed in the post-marketing setting based on these laboratory findings. CPK elevation was the most common adverse reaction leading to dose reduction of brigatinib in the ALTA study. • Severe and life threatening pulmonary toxicity, including pneumonitis (lung inflammation), is a potential risk. Grade 3 or 4 (severe) pulmonary adverse reactions occurred in 3% of patients during the first 9 days of treatment in the ALTA study and 5.5% of patients experienced pneumonitis at any point during treatment. • Visual toxicity can also occur; however, severe toxicity was uncommon (one patient with Grade 3 cataract and one with Grade 3 macular edema). • Because safety data were obtained in trials that did not include a non-brigatinib comparator arm, uncertainty exists in regards to the contribution of brigatinib to observed toxicities because many of the toxicities also occur in patients with advanced lung cancer (for example, cough and dyspnea).	dose modification. Some uncertainty regarding risk will be addressed through additional data obtained from the post-marketing requirement trial comparing brigatinib to crizotinib in the first-line setting.
Risk Management	• Risks will be communicated in product labeling and in patient labeling. • A Risk Evaluation and Mitigation Strategy (REMS) is not needed to ensure that the benefits of brigatinib outweigh its risks. • The subpart H (Accelerated Approval) postmarketing requirement (PMR) will provide additional safety data to further refine the risk profile of brigatinib. The PMR consists of Study AP26113-13-301 which will assess the effects of brigatinib versus crizotinib in patients with ALK-positive NSCLC. • Uncertainty exists regarding the appropriate dose of brigatinib in patients with moderate to severe liver impairment, severe kidney impairment, or who are receiving drugs that affect a liver enzyme called CYP3A4 (this enzyme that can metabolize (break down) certain drugs). This uncertainty	Although brigatinib can cause severe/serious toxicities, brigatinib will be prescribed by oncologists who by training understand how to monitor, identify, and manage such toxicities. Such an approach is standard in the practice of medical oncology.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	will be addressed through postmarketing commitments or requirements (see Section 6 of this review).	

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Steven Lemery, M.D., M.H.S.
CDTL

2 Therapeutic Context

2.1. Analysis of Condition

Lung cancer is the leading cause of cancer death in the United States (U.S.) and developed world for both men and women. In the U.S., an estimated 224,390 new cases of lung cancer will be diagnosed in 2016 and approximately 158,080 deaths will occur (Siegal, Miller, et al. 2016). Non-small cell lung cancer (NSCLC) is the predominant histology, comprising 85% of all patients diagnosed with lung cancer. Eighty-four percent of cases are diagnosed in advanced stages, and for patients with distant metastases, the 5-year survival rate is 4% (American Lung Association Lung Cancer Fact Sheet).

The first description of a fusion oncogene consisting of the anaplastic lymphoma kinase (ALK) gene and the echinoderm microtubule-associated protein-like 4 (EML4) gene in NSCLC cells was published in 2007. The ALK rearrangement resulted in an EML4-ALK fusion protein kinase which demonstrated the potential to cause malignant transformation in animal models (Soda, Choi, et al. 2007). A previously developed ALK kinase inhibitor demonstrated activity against ALK rearrangement-containing cell lines in vitro (Koivunen, Mermel, et al. 2008) and in vivo against tumors occurring in a transgenic mouse model expressing the EML4-ALK fusion protein, specifically in lung alveolar epithelial cells (Soda, Takada, et al. 2008).

ALK rearrangements are detected in 3-7% of all patients with NSCLC (Camidge, Pao, et al. 2014) in both Asia and the West (Soloman, Varella-Garcia, et al. 2009). Clinicopathologic features that occur with ALK-rearranged (also referred to as ALK-positive) NSCLC are younger age, light or never smoking status, adenocarcinoma histology, and absence of response to epidermal growth factor receptor (EGFR) inhibitors (Shaw, Yeap, et al. 2009). Crizotinib, an oral tyrosine kinase inhibitor against multiple targets including ALK, was approved in 2011 for the treatment of patients with ALK-positive metastatic NSCLC. The initial approval of crizotinib was based on early reports from 2 multicenter single arm studies of crizotinib in a total of 255 patients with advanced NSCLC demonstrating objective response rates (ORRs) of 50% and 61%. The majority of patients in these studies had metastatic disease (95%) and received prior systemic treatment for locally advanced or metastatic disease (94%) (U.S. Prescribing Information [USPI] crizotinib 8/2011). The crizotinib USPI was later updated with the results of a randomized trial comparing crizotinib to chemotherapy (pemetrexed or docetaxel) in 347 patients with metastatic ALK-positive NSCLC previously treated with one platinum-based chemotherapy regimen and demonstrated an improvement in median progression-free survival (PFS) for patients treated with crizotinib (7.7 months vs 3.0 months; hazard ratio [HR] 0.49 [95% confidence interval {CI} 0.37, 0.64]) (USPI crizotinib 11/2013). The crizotinib USPI was further updated with results from a randomized trial of crizotinib compared to pemetrexed-platinum combination chemotherapy in 343 patients with ALK-positive nonsquamous NSCLC who had not received any previous systemic therapy for advanced NSCLC. There was a significant improvement in median PFS for

patients in the crizotinib arm (10.9 months vs 7.0 months; HR 0.45 [95% CI 0.35, 0.60]) (USPI crizotinib 11/2013), and crizotinib is currently considered standard of care for the first-line therapy of ALK-positive NSCLC (National Comprehensive Cancer Network [NCCN] guidelines: Non-small cell lung cancer v7 2015).

Tumors may develop resistance to crizotinib during treatment; mechanisms of resistance include acquisition of a secondary mutation in the ALK tyrosine kinase domain, amplification of the fusion gene, or alternative signaling pathways (Matikas, Kentepozidis, et al. 2016). Another important factor in the treatment of NSCLC is the development of brain metastases. A retrospective analysis of two studies of patients with advanced ALK-positive NSCLC reported that 20% of patients without brain metastases at the time of enrollment who experienced PD in target lesions subsequently developed brain metastases while receiving crizotinib. Furthermore, 70% of patients with pre-existing brain metastases who experienced PD had new sites or progression of pre-existing lesions in the brain during treatment with crizotinib (Costa, Shaw, et al. 2015).

2.2. Analysis of Current Treatment Options

Two marketed orally-administered tyrosine kinase inhibitors for this population are ceritinib and alectinib which received accelerated approval in 2014 and 2015, respectively (USPI ceritinib 4/2014 and USPI alectinib 12/2015). These drugs are not considered available therapy, as defined in FDA Guidance for Industry: Expedited Programs for Serious Conditions - Drugs and Biologics, because they have not received regular approval.

Other options for ALK-positive NSCLC patients with progression of disease on crizotinib include the anti-programmed death-1 (anti PD-1) monoclonal antibodies pembrolizumab and nivolumab as well as standard first-line chemotherapy usually consisting of a platinum doublet which is standard of care for the unselected NSCLC population (NCCN guidelines: Non-small cell lung cancer v7 2015).

Ceritinib was granted accelerated approval in 2014 based on results of a multicenter single arm study in 163 patients with metastatic ALK-positive NSCLC who progressed on or were intolerant to crizotinib. The results demonstrated an ORR of 44% (95% CI 47%, 62%) as assessed by Blinded Independent Central Review Committee (BIRC) with a median DoR of 7.4 months (95% CI 5.4, 10.1). Approximately 60% of patients initiating treatment with ceritinib at the recommended dose of 750 mg daily required at least one dose reduction, and dose modification related to gastrointestinal toxicities of nausea, vomiting, diarrhea or abdominal pain occurred in 38% of patients (USPI ceritinib 4/2014).

Alectinib was granted accelerated approval in 2015 based on results of two single-arm multicenter studies in a total of 225 patients who had progressed on or were intolerant to crizotinib. Results showed ORRs of 38% (95% CI 28%, 49%) and 44% (95% CI 36%, 53%) as assessed by Independent Central Review (IRC). Median DoR was 7.5 months (95% CI 4.9, not

estimable [NE]) and 11.2 (95% CI 9.6, NE). Dose reductions due to adverse reactions occurred in 23% of patients initiating treatment at the recommended dose (USPI alectinib 12/2015).

Pembrolizumab was granted accelerated approval in October 2015 for patients with metastatic NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for ALK or EGFR mutations and any evidence of PD-L1 expression by a clinical trial immunohistochemistry assay (USPI pembrolizumab 10/2015). In October 2016, traditional approval was granted based on results from a randomized, multicenter, open-label study in which 1033 patients whose tumors had PD-L1 expression of 1% or greater were randomized 1:1:1 to receive one of two doses of pembrolizumab or docetaxel. The results demonstrated an improvement in median overall survival (OS) for patients treated with the recommended dose of 2 mg/kg every 3 weeks (10.4 months vs 8.5 months; HR 0.71 (95% CI 0.58, 0.88). The ORR of pembrolizumab in patients with a PD-L1 tumor proportion score of ≥ 1% was 18% (95% CI: 14, 23) in the 2 mg/kg arm compared to 19% (95% CI: 15, 23) in the 10 mg/kg arm. Pembrolizumab was discontinued due to adverse reactions in 14% of patients. The primary toxicities of concern are related to the class of drug and include immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and infusion-related reactions (USPI pembrolizumab 10/2016).

Initially approved for metastatic NSCLC squamous histology only, nivolumab was subsequently approved for NSCLC unselected by histology in October 2015 for patients with progression on or after platinum-based chemotherapy, and for those with EGFR or ALK genomic tumor aberrations, after progression on FDA-approved therapy for these aberrations. Approval was based on results of a randomized open-label multicenter trial in which 582 patients received either nivolumab or docetaxel. The ORR of nivolumab for second-line treatment of metastatic non-squamous NSCLC that included patients with ALK mutations was 19% (95% CI: 15, 24) compared to 12% (95% CI: 9,17) in the docetaxel arm. Median OS demonstrated an improvement in patients treated with nivolumab (12.2 months vs 9.4 months; HR 0.73 (95% CI 0.60, 0.89). Nivolumab was discontinued in 13% of patients for an adverse reaction (USPI nivolumab 10/2015). The primary toxicities of concern are due to class-effect and are described in the previous paragraph.

Finally, chemotherapy (including platinum-based doublets) in patients who are chemotherapy-naïve is another standard of care option in the U.S. for ALK-NSCLC patients with progression of disease on crizotinib. Median OS observed for first-line treatment with platinum-based combination chemotherapy in earlier studies, which included patients with NSCLC regardless of histology, ranged from approximately 8 to 11 months with response rates of 15% to 32% (Ramalingam and Belani 2008). A subsequent randomized study comparing cisplatin plus pemetrexed to cisplatin plus gemcitabine for the first-line treatment of NSCLC demonstrated response rates close to 30% in both arms; this study included a pre-specified analysis of OS by histology, and the median OS for the subset of patients with adenocarcinoma histology receiving cisplatin plus pemetrexed was 12.6 months (Scagliotti, Parikh, et al. 2008). In a randomized trial comparing crizotinib to platinum-based combination chemotherapy for the first-line treatment of advanced ALK-positive NSCLC, the ORR observed in the chemotherapy

arm was 45% with a median progression-free survival (PFS) of 7.0 months (Soloman, Mok, et al. 2014). These findings are based on the treatment of patients who have received no prior systemic therapy for advanced NSCLC. Another study randomized patients with ALK-positive NSCLC who had already received one prior platinum-based regimen to treatment with crizotinib versus either pemetrexed or docetaxel and demonstrated ORR of 20% in the chemotherapy arm (Shaw, Kim, et al. 2013). There is insufficient data available to determine the potential impact of prior treatment with crizotinib on response to treatment with platinum-based combination chemotherapy. Predominant toxicities associated with the chemotherapy regimens most commonly used for NSCLC include hematologic toxicities (e.g., cytopenias), gastrointestinal toxicities (e.g., nausea, vomiting), and neurotoxicity (e.g., peripheral neuropathy with taxanes, ototoxicity with cisplatin).

There is currently an unmet medical need for patients with ALK-positive metastatic NSCLC who experience disease progression on or intolerance to crizotinib. Without further treatment, patients who progress on crizotinib are expected to have median survival of approximately 9 months (Ou, Jänne, et al. 2014) and all patients will die of their disease.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Brigatinib is a new molecular entity (NME) and is not currently marketed in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

Following a pre-IND meeting held on May 24, 2011, regarding the first-in-human trial and clinical development plans for brigatinib (AP26113) under IND 110935, the original IND was filed on June 28, 2011, by ARIAD Pharmaceuticals, Inc. A list outlining the pertinent regulatory history for brigatinib is included in Table 1.

Table 1: Regulatory History for Brigatinib

Date	Description
March 18, 2013	Type B, End-of-phase 1 meeting to discuss the clinical development program for AP26113 and the design of the randomized non-comparative trial (Study AP26113-13-201)
October 24, 2013	Type B Pre-phase 3 meeting to discuss the design of the proposed confirmatory trial, Study AP26113-13-301) comparing the safety and efficacy of brigatinib to crizotinib in the first-line treatment of ALK-positive NSCLC
October 1, 2014	Breakthrough Therapy Designation granted for the treatment of patients with ALK-positive NSCLC whose tumors are resistant to crizotinib
June 30, 2015	Type B multidisciplinary post-Breakthrough Designation meeting
October 30, 2015	FDA feedback to proposed Early Onset Pulmonary Event case definition
March 2, 2016	Type B pre-NDA meeting to discuss the content and format of the Quality information to be submitted in the NDA, including discussion of the proposed commercial dissolution procedure, proposed drug product specifications, and the proposed shelf life
April 15, 2016	Type B pre-NDA meeting to discuss the results from Studies AP26113-11-101 and AP26113-13-201 and to reach agreement on the content and format of the proposed NDA
April 28, 2016	Orphan Drug Designation granted for treatment of ALK-positive, c-ros 1 oncogene (ROS1)-positive, or EGFR-positive NSCLC
May 25, 2016	Rolling Review granted

In the March 18, 2013, meeting, FDA stated that the proposed study may not be feasible if patients are required to have received one to three lines of prior chemotherapy as well as crizotinib. FDA stated that it would be acceptable to enroll patients who received prior crizotinib irrespective of the number of lines of prior chemotherapy. FDA also stated that the

single arm trial (assessing ORR) could provide a reasonable estimate of the treatment effect and could support accelerated approval if the benefit-risk assessment is favorable. FDA also provided advice in regards to overall development program (e.g., confirmatory trial).

During the June 30, 2015, Type B meeting, FDA provided general agreement in regards to the time line and schedule for a rolling NDA; however, FDA requested an updated safety analysis in the IB to be submitted by September 2015. FDA could not reach agreement upon the contents of the NDA without reviewing summary data from ALTA to be included in the NDA. Such agreements would be reached during the Type B, pre-NDA meeting. FDA and ARIAD also discussed bridging data that would be necessary to support approval of both the 30 mg and 90 mg strengths, and that, in general, the completed and planned pharmacology, safety pharmacology, and toxicology studies described in the meeting package appeared sufficient to support an NDA filing.

During the April 15, 2015, Type B, pre-NDA meeting, FDA agreed that ARIAD's proposed data package appeared acceptable. FDA requested an assessment of DDI risk; and exposure-response analyses from ALTA. Agreement was reached regarding the contents of a complete application and that a REMS would not be necessary for FDA to file the application.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI found that the primary efficacy endpoint, objective response rate (ORR) as determined by the clinical investigators, to be verifiable at four inspected clinical sites. OSI found no significant inspectional findings for the four investigators. The study's sponsor, ARIAD, was also inspected and received an inspection designation of NAI (no action indicated).

Results of the independent review of radiographs, however, could not be verified because of a lack of an apparent audit trial during the inspection for a substantial number of changes made to imaging data (refer to OSI review). FDA held a telephone conference with ARIAD on February 9, 2017, to discuss these findings and as a follow-up to a February 7, 2017, FDA request for information regarding the independent review. An additional telephone conference was held on March 10, 2017 to discuss source documentation regarding the changes in the database and reasons for the changes (which were not able to be accessed during the time of the inspection). ARIAD had earlier clarified that only one patient with data changes had a change in response classification (from best overall response of a responder to a non-responder).

On March 13, 2017, ARIAD submitted additional information requested by FDA during the March 10, 2017 teleconference relating to source documentation for the changes made to the IRC database. After reviewing this additional documentation, the OSI reviewer concluded that the issues relating to IRC database integrity had been resolved and that the IRC-generated efficacy data submitted to the application appear reliable.

4.2. Product Quality

Novel excipients: No
Any impurity of concern: No

Please see FDA CMC review for further details. Per the CMC reviewer, there are no identified CMC deficiencies.

4.3. Clinical Microbiology

Please see FDA product quality microbiology review for further details. There are no currently identified microbiology issues.

4.4. Devices and Companion Diagnostic Issues

Eligibility for the pivotal studies covered by this review included the requirement for documentation of ALK rearrangement in tumor tissue confirmed by an FDA-approved test.

There are no issues of concern related to the use of this test to select patients appropriate for treatment with brigatinib.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Brigatinib (AP26113) is a tyrosine kinase inhibitor that has activity against multiple kinases including anaplastic lymphoma kinase (ALK), ROS1, insulin-like growth factor receptor-1 (IGF-1R), and FLT-3 as well as EGFR with deletion and point mutations at concentrations that have been achieved at the 180 mg dose level used in clinical trials conducted to support the approval of the drug (Cmax of approximately 1450 ng/mL or 2482 nM). In an in vitro kinase screen, brigatinib inhibited ALK, a receptor tyrosine kinase involved in neuronal cell differentiation and regeneration, with an IC_{50} of 0.6 nM. Translocations involving the ALK tyrosine kinase domain, such as ALK fused to the echinoderm microtubule-associated protein like protein 4 (EML4), result in fusion proteins with dysregulated expression and constitutive tyrosine kinase activity. The main metabolite of brigatinib, AP26123, inhibited ALK with ≤4-fold lower potency than brigatinib in in vitro kinase and cellular assays, though AP26123 was not considered a major metabolite in humans (≤10% of parent). Brigatinib also exhibited activity against the non-selective sigma receptor and the sodium ion channel in an in vitro secondary pharmacology screen.

The Applicant examined downstream signaling effects of brigatinib only on the ALK pathway. Treatment with brigatinib inhibited in vitro and in vivo phosphorylation of ALK and the downstream signaling proteins AKT, ERK1/2, S6, and STAT3 in human NSCLC cell lines expressing EML4-ALK, resulting in inhibition of in vitro cellular and anchorage-independent growth, but did not inhibit downstream ALK signaling in ALK-negative cell lines. In keeping with these findings, brigatinib exhibited dose-dependent anti-tumor activity in mice bearing subcutaneous (s.c.) human EML4-ALK-positive NSCLC xenografts. Brigatinib also prolonged mouse survival in an in vivo NSCLC orthotopic brain tumor model, suggesting that the drug can penetrate the blood brain barrier at levels sufficient for activity.

At concentrations that have been clinically achieved at the 180 mg dose level, brigatinib inhibited the in vitro viability of Ba/F3 cells expressing 17 secondary ALK mutations associated with resistance to approved ALK inhibitors. Further, brigatinib exhibited dose-dependent in vivo anti-tumor activity against Ba/F3 xenografts expressing four crizotinib-resistant ALK mutations (L1196M, G1269S, S1206R, and G1202R). Based on IC_{50} values, brigatinib inhibited the epidermal growth factor receptor (EGFR) mutations Del (E746-A750), L858R, Del/T790M, and L858R/T790M, but not wild-type EGFR, in in vitro cellular assays at concentrations that have been achieved clinically at the recommended dose. Brigatinib also exhibited in vitro activity against secondary mutations in ROS1 (L2026M) and FLT3 (F691L and D835Y) at clinically achievable concentrations based on IC_{50} values.

Brigatinib inhibited the hERG potassium current with an IC_{50} >10 µM, which is not clinically achievable at the recommended dose of 180 mg. In keeping with this, brigatinib did not induce

QTcB prolongation in a single-dose safety pharmacology study in cynomolgus monkeys or in the 6-month repeat-dose study in monkeys. Single oral administration of brigatinib at dose levels ≥300 mg/m^2 resulted in an increased incidence of ptosis in Sprague-Dawley rats compared to controls, but did not adversely affect central nervous system (CNS) parameters at dose levels up to 600 mg/m^2.

The Applicant conducted repeat-dose toxicology studies of up to 6 months in rats and monkeys to investigate the safety of brigatinib. In the 6-month study, daily oral administration of brigatinib (AP26113) to Sprague Dawley rats at dose levels of 7.5, 15, and 25 mg/kg/day daily resulted in treatment-related mortalities in animals treated at doses ≥15 mg/kg (approximately 0.3 times the exposure measured by AUC at the 180 mg clinical dose) due to cardiac toxicity, described as myocardial degeneration or acute hemorrhage or to chronic renal lesions consisting of moderate to marked tubular dilation with degeneration and protein casts and glomerulonephritis. Clinical observations noted in animals found dead and/or euthanized in extremis included tonic convulsion, labored respiration, and hypoactivity. Additional target organs included the liver (increased mean liver enzymes and necrosis), male reproductive organs (testicular degeneration and reduced sperm), and pancreas (acinar atrophy). Ocular toxicities including cataract (bilateral) and retinal degeneration occurred in dose- and time-dependent manner. Visual disturbances and pancreatic toxicity have been reported clinically.

In the 6-month toxicology study in monkeys, administration of brigatinib at the high dose of 15 mg/kg (with exposures below the clinical exposure at the 180 mg dose based on AUC) resulted in mortality attributed to inflammation of the lungs and pericardium. Consistent with cardiac effects seen in longer term studies, single dose oral administration of brigatinib in monkeys at doses of 10, 20, and 30 mg/kg resulted in statistically significant decreases in mean heart rate and pulse pressure at 1-6 hrs post-dose compared to controls; delayed effects, primarily at the 30 mg/kg dose level, included statistically significant increases in heart rate, blood pressure, body temperature, and respiratory frequency compared to controls. The delayed effects were generally seen at brigatinib exposures within ~0.6- to 2-fold of those achieved clinically at the 180 mg dose level (approximately 20276 ng*h/mL based on AUC). Bradycardia, hypertension, and pulmonary toxicity have been observed clinically with brigatinib. Other drug-related findings in the 6 month monkey study included reduced lymphocyte counts, reduced reticulocyte counts, and lower spleen, testes, and pituitary gland weights. Additional target organs included the kidneys (granular pigment), lymph nodes (reduced cellularity), thymus (reduced cellularity and weight), and lungs (alveolar macrophages).

The Applicant did not conduct carcinogenicity studies and these studies are not required to support a marketing application for a drug intended to treat patients with advanced cancer. Brigatinib was not genotoxic in the Ames test or in vitro mammalian chromosome aberration test in the absence or presence of S9 mix but showed dose-dependent chromosomal damage (aneugenic effects) in the in vivo mammalian erythrocyte micronucleus test. Because of this finding, FDA initially proposed that the brigatinib label include recommendations stating that females of reproductive potential should use effective contraception during brigatinib

treatment and for 6 months following the last dose and that males with female partners of reproductive potential should use effective contraception during brigatinib treatment and for 3 months following the last dose. The advice for females of reproductive potential to use effective contraception for 6 months following completion of brigatinib treatment was based on a draft guidance for labeling under development in the Office of Hematology Oncology Products. The Applicant argued that recommendations for duration of contraception in the brigatinib label should be consistent with recommendations included in product labeling for approved drugs of the same class (i.e., that brigatinib product labeling should include a recommendation for women of reproductive potential to continue use of effective contraception for 4 months following discontinuation of brigatinib). Due to residual uncertainty regarding the necessary duration of contraception and the fact that the reproductive guidance is not currently available to the public, the proposal to limit the duration of contraception for females of reproductive potential to 4 months following discontinuation of brigatinib was considered acceptable to FDA. The Applicant did not evaluate transfer of brigatinib to the fetus or milk. As a result, it is advised that women do not breastfeed during treatment with brigatinib or for 1 week following the final dose.

In an embryofetal toxicology study, oral gavage administration of brigatinib at 5, 12.5, and 25 mg/kg/day to pregnant rats on during the period of organogenesis (gestation days 6-17) did not result in maternal mortality; however, there were marked increases in post-implantation loss, including total resorption at the 25 mg/kg level (approximately 1.26 times the human exposure measured by AUC at the 180 mg dose) as well as dose-dependent decreases in fetal weights at doses ≥ 12.5 mg/kg (approximately 0.7 times the human exposure at 180 mg). Dose-related skeletal (incomplete ossification, small incisors) and visceral (small tongue, small hindlimb, hyperflexion) alterations occurred at doses as low as 12.5 mg/kg. Treatment-related external, visceral and skeletal malformations occurred at 25 mg/kg/day and included anasarca (generalized subcutaneous edema), anophthalmia (absent eyes), forelimb hyperflexion, small, short and/or bent limbs, multiple fused ribs, bent scapulae, omphalocele (intestine protruding into umbilicus), and gastroschisis (intestines protruding from herniated abdominal wall) as well as moderate bilateral dilatation of the lateral ventricles. These findings support the inclusion of a warning for embryo-fetal toxicity in the brigatinib label.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Primary pharmacology

A. In Vitro Studies

The Applicant evaluated the selectivity of AP26113 (brigatinib) by testing its in vitro activity against 293 human protein kinases (266 unique kinases and 27 mutants) using a radiometric binding assay with 10 µM ATP (Kinase Hotspot by Reaction Biology Corporation; Study #

ARP227). Incubation with 1 µM AP26113 inhibited 36/293 kinases (12%) by ≥90%, 67/293 kinases (23%) by ≥75%, and 196/293 kinases (67%) by <50%. IC_{50} values were then determined for 93 of these kinases. AP26113 had highest activity against ALK, with an IC_{50} of 0.6 nM (Table 2). AP26113 also inhibited 11 other kinases with IC_{50} values <10 nM. AP26113 was approximately 122- and 267-fold more specific for ALK than insulin-like growth factor receptor-1 (IGF-1R) and insulin receptor (InsR), respectively, other members of the insulin receptor superfamily. AP26113 inhibited c-MET with an IC_{50} value >1000 nM in the initial 293 kinase assessment, so it was not analyzed further. Overall, AP26113 inhibited 81 kinases at IC_{50} concentrations that have been achieved clinically at the 180 mg dose level of brigatinib (free C_{max} at the 180 mg clinical dose is approximately 853 nM based on ~66% protein binding). The Applicant also investigated the activity of brigatinib's main metabolite, AP26123. Compared to brigatinib, AP26123 exhibited relatively similar potency (0.8- to 4.6-fold) against all 8 kinases (ALK, HER4, EGFR-L858R, EGFR-L858R/T790M, IGF-1R, HER2, EGFR, and InsR) tested.

Table 2: In Vitro Effects of Brigatinib on 93 Human Protein 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/SNF1LK2/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	IR	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				

(Applicant Table reproduced from Study # ARP227)

In a fourth screen, the Applicant demonstrated that brigatinib inhibited the in vitro activity of 14 ALK variants with IC_{50} values ≤5 nM (see Table 3). These included 12 secondary mutations in the kinase domain, many of which have been associated with clinical resistance to the ALK inhibitor crizotinib and/or the second generation ALK inhibitors ceritinib and alectinib. To investigate the binding of brigatinib to ALK, the Applicant employed X-ray crystallography at 2Å resolution and demonstrated that brigatinib adopts a U-shaped ligand conformation to bind the ATP-binding site, with the dimethylphosphine oxide moiety fostering intra-molecular interactions through an O···NH hydrogen bond (Study # ARP626). Comparison of the ALK-

brigatinib co-structure to that of crizotinib, ceritinib, and alectinib revealed different molecular interactions potentially reflective of differences in potency and/or susceptibility to secondary resistance mutations (data not shown).

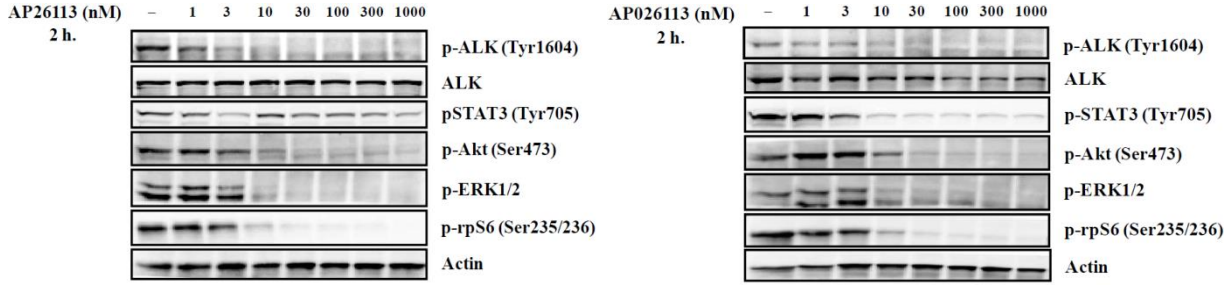
Table 3: In vitro Effects of Brigatinib on ALK Variants

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

(Applicant Table reproduced from Study # ARP227)

In vitro pharmacology studies using human H3122 and H2228 NSCLC cell lines expressing the EML4-ALK fusion protein demonstrated that incubation with AP26113 for 2 hours inhibited ALK phosphorylation at tyrosine (Tyr) 1604 in with IC_{50} values of approximately 4 nM (Study # ARP195). As shown in Figure 1, AP26113 also inhibited phosphorylation of the downstream ALK signaling proteins AKT, ERK1/2, S6, and STAT3 in a concentration-dependent manner. Similarly, AP26113 inhibited phosphorylation of ALK (IC_{50} values = 1.5 to 12 nM), AKT, ERK1/2, S6, and STAT3 in five anaplastic large cell lymphoma (ALCL) cell lines expressing nucleophosmin (NPM)-ALK fusions (Study # ARP193; data not shown). Crizotinib was ~10-fold less potent compared to AP26113 at inhibiting ALK and its downstream signaling pathways in the EML4-ALK positive NSCLC cell lines and NPM-ALK positive ALCL cell lines tested. As expected, AP26113 did not inhibit downstream ALK signaling in ALK-negative ALCL or NSCLC cell lines.

Figure 1: Effect of Brigatinib on Downstream ALK Signaling in EML4-ALK positive NSCLC Cells

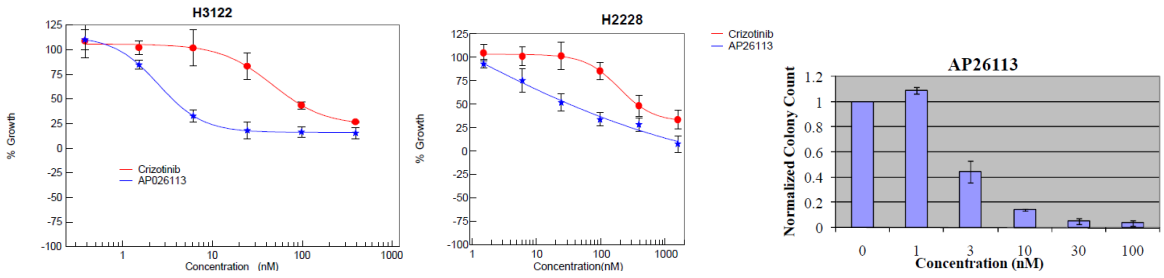


Left: H3122 cells; Right: H2228 cells; (Applicant Figure reproduced from Study # ARP195)

Incubation with AP26113 for 3 days inhibited the growth of the EML4-ALK positive NSCLC cell lines H3122 and H2228 with 50% growth inhibition (GI_{50}) values of 4.2 nM and 10.1 nM (Figure 2), respectively, but had reduced potency in two ALK-negative NSCLC cell lines (GI_{50} values of 503 nM and 1337 nM; Study # ARP194). Based on GI_{50} values, crizotinib was >10-fold less potent against H3122 and H2228 cells compared to AP26113. Further, as measured by 4 weeks of colony formation in soft agar, treatment with AP26113 inhibited anchorage-independent growth of H2228 cells with an IC_{50} value of 2.4 nM, compared to an IC_{50} value of >100 nM in an

ALK-negative cell line. Crizotinib was 36-fold less potent (IC_{50} = 86.7 nM) against H2228 cells compared to AP26113.

Figure 2: Effect of Brigatinib on In Vitro Cellular and Anchorage-Independent Growth of ALK-Positive NSCLC Cells



Left/middle: cellular growth measured by CyQuant; Right: anchorage-independent growth in H2228 cells; (Applicant Figure reproduced from Study # ARP194)

Similarly, AP26113 inhibited the in vitro growth of five ALCL cell lines expressing NPM-ALK in a concentration-dependent manner with GI_{50} values ranging from 8.8 nM to 30.8 nM (Study # ARP192; data not shown). Based on GI_{50} values, the AP26113 metabolite AP26123 and crizotinib were ~1.3- to 4-fold and ~10-fold less potent, respectively, against ALK-positive cells compared to AP26113.

Clinically, resistance to ALK inhibitors is a common finding, driven by mutations in the ALK kinase domain following treatment with approved agents. The Applicant investigated the activity of brigatinib inhibition of resistance mutants in several studies. In order to identify novel mutations in the ALK kinase domain associated with resistance to AP26113, crizotinib, ceritinib, and alectinib, the Applicant performed an in vitro mutagenesis screen using the DNA-modifying agent N-ethyl-N-nitrosourea to create mutants in Ba/F3 cells generated to depend on EML4-ALK for survival (Study # ARP617). Mutated cells were then incubated with crizotinib (500, 750, 1000, and 1500 nM), AP26113, ceritinib, or alectinib (100, 200, 500, 1000, and 1500 nM). Cell outgrowth was monitored for up to 5 weeks, and the kinase domain of ALK was sequenced from surviving cells in order to identify ALK secondary mutations. Incubation with 100 nM AP26113 yielded S1206A, F1174C/V/I/L, I1171N, and E1210K ALK mutations; at 200 nM L1196M was also detected. Notably, incubation with ≥500 nM AP26113 suppressed the emergence of ALK secondary resistance mutations in two independent assays, whereas higher concentrations of crizotinib (1500 nM), ceritinib (1000 nM), and alectinib (1500 nM) were required to suppress the emergence of mutations. The in vitro screen identified three novel ALK secondary mutations not previously associated with clinical resistance to crizotinib, ceritinib, or alectinib: E1210K, L1198F, and V1180L. Thus, although ALK secondary mutations emerged following incubation with ≤200 nM AP26113, there were no ALK mutations associated with resistance to AP26113 at concentrations ≥500 nM, which are clinically achievable at the recommended 180 mg dose level of brigatinib.

In Study # ARP618, the Applicant investigated the in vitro activity of AP26113 in a panel of Ba/F3 cell lines stably transduced with wild-type (WT) EML4-ALK or EML4-ALK expressing secondary kinase domain ALK mutations that have been associated with resistance to crizotinib, ceritinib, and/or alectinib. Untransformed Ba/F3 cells were used as a negative control. As assessed using the MTS assay, incubation with AP26113 for 3 days inhibited the proliferation of all 17 EML4-ALK mutant cell lines with IC_{50} values ranging from 9 nM to 184 nM (Table 4).

Table 4: Effect of Brigatinib and other ALK Inhibitors on the In Vitro Viability of Ba/F3 cells Expressing WT or Mutant EML4-ALK Fusion Kinases

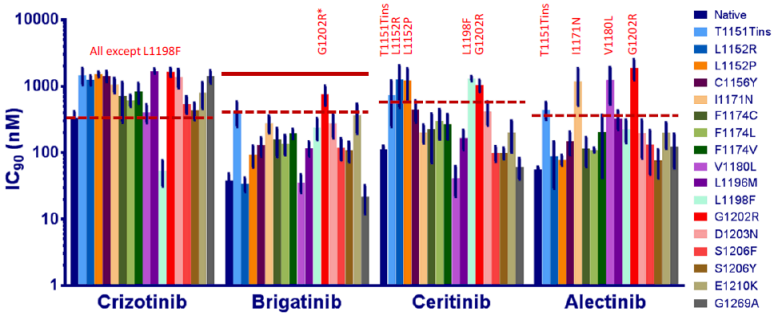
	IC50 ± SD (nM)				IC90 ± SD (nM)			
ALK Variant	Crizotinib	Brigatinib	Ceritinib	Alectinib	Crizotinib	Brigatinib	Ceritinib	Alectinib
Native	107 ± 11	14 ± 1	37 ± 8	25 ± 8	331 ± 87	38 ± 10	112 ± 15	56 ± 5
T1151Tins	1109 ± 453	114 ± 39	283 ± 97	201 ± 12	1469 ± 413	416 ± 169	734 ± 486	444 ± 130
L1152R	844 ± 100	11 ± 2	437 ± 216	62 ± 9	1247 ± 206	34 ± 8	1270 ± 790	88 ± 59
L1152P	721 ± 141	20 ± 7	451 ± 170	48 ± 8	1528 ± 129	94 ± 34	1227 ± 624	78 ± 14
C1156Y	529 ± 152	45 ± 19	195 ± 70	67 ± 33	1421 ± 266	129 ± 41	449 ± 160	149 ± 57
I1171N	532 ± 122	124 ± 36	119 ± 42	724 ± 130	1058 ± 258	278 ± 80	201 ± 62	1191 ± 681
F1174C	238 ± 128	58 ± 27	109 ± 70	31 ± 13	718 ± 432	160 ± 73	229 ± 159	116 ± 55
F1174L	253 ± 90	55 ± 21	117 ± 53	44 ± 10	618 ± 124	137 ± 45	304 ± 145	110 ± 8
F1174V	257 ± 101	64 ± 11	121 ± 55	46 ± 19	834 ± 282	195 ± 33	271 ± 110	206 ± 164
V1180L	170 ± 47	11 ± 3	16 ± 6	597 ± 172	406 ± 123	36 ± 11	42 ± 20	1235 ± 700
L1196M	589 ± 97	41 ± 14	67 ± 17	133 ± 55	1707 ± 138	118 ± 30	166 ± 55	327 ± 105
L1198F	17 ± 6	82 ± 41	697 ± 167	84 ± 45	54 ± 23	242 ± 88	1316 ± 110	226 ± 85
G1202R	617 ± 76	184 ± 45	354 ± 73	695 ± 260	1638 ± 236	762 ± 249	1042 ± 214	1886 ± 651
D1203N	459 ± 176	79 ± 31	159 ± 76	42 ± 19	1370 ± 426	276 ± 109	420 ± 164	196 ± 114
S1206F	199 ± 61	43 ± 17	39 ± 17	34 ± 11	542 ± 155	120 ± 42	99 ± 25	133 ± 86
S1206Y	179 ± 62	36 ± 16	42 ± 13	19 ± 8	435 ± 127	109 ± 36	99 ± 19	77 ± 36
E1210K	240 ± 79	107 ± 38	80 ± 27	59 ± 27	798 ± 340	366 ± 171	202 ± 101	200 ± 85
G1269A	509 ± 146	9 ± 5	29 ± 15	56 ± 19	1413 ± 306	22 ± 10	61 ± 21	125 ± 66
Parental*	1237 ± 241	3214 ± 725	1666 ± 759	2067 ± 1395	2088 ± 262	9502 ± 997	2841 ± 2239	7461 ± 3033

*: Untransformed Ba/F3 cells; Brigatinib = AP26113; (Applicant Figure reproduced from Study # ARP618)

The Applicant then conducted an exploratory analysis of these in vitro findings using clinical pharmacology data from brigatinib and estimated C_{max} levels based on publically available data at the approved doses for crizotinib, ceritinib, and alectinib. As expected, using total C_{max} values for these products over-predicted their clinical activity against ALK mutants based on the values in Table 4; however, the free C_{max} levels calculated using human plasma protein binding data generally under-predicted their activity against WT and/or mutant ALK. As a result, the Applicant assessed the functional impact of plasma protein binding on drug activity by comparing the IC_{50} values for inhibition of viability of Ba/F3 cells driven by ALK in the presence or absence of physiological concentrations of human serum albumin and alpha 1-acid glycoprotein. The analysis suggested the highest correlation with clinical activity when the "effective" C_{max} values corrected for the functional effects of protein binding were compared to in vitro IC_{90} values rather than IC_{50} values. The calculated "effective" C_{max} values following once

daily dosing with 90 mg and 180 mg brigatinib were 473 nM and 1243 nM, respectively, which exceed the IC_{90} values for WT ALK, 16/17 ALK mutants at 90 mg (not G1202R), and 17/17 ALK mutations at 180 mg (see Figure 3). Brigatinib is also expected to inhibit WT ALK and the ALK mutations tested at free drug concentrations achievable at the recommended dose of brigatinib (free C_{max} = 324 nM at 90 mg and 853 nM at 180 mg).

Figure 3: IC_{90} Values Relative to "Effective" C_{max} Values for Brigatinib



Horizontal lines represent "effective" C_{max} values in patients; dotted line: 90 mg; solid line: 180 mg
(Applicant Figure reproduced from Study # ARP618)

The Applicant also investigated the effects of AP26113 on ROS1 signaling. As assessed using the MTS assay, AP26113 inhibited the in vitro viability of Ba/F3 cells expressing one of three native ROS1 fusion variants (CD74-ROS1, FIG-ROS1, or SDC4-ROS1) with IC_{50} values ranging from 16 to 31 nM and IC_{90} values ranging from 41 to 91 nM (Study # ARP622; data not shown). Western blot analysis demonstrated that AP26113 induced concentration-dependent inhibition of phosphorylated ROS1, AKT, and ERK1/2 in Ba/F3 cells expressing CD74-ROS1. Further, AP26113 retained its in vitro activity against CD74-ROS1 containing the secondary kinase domain gate keeper mutation L2026M (IC_{50} of 17 nM vs 18 nM for WT; IC_{90} of 34 nM vs 71 nM for WT) in growth assays, whereas the potency of crizotinib was reduced ≤5-fold compared to native CD74-ROS1 (IC_{50} of 127 vs. 25 nM for WT; IC_{90} of 251 nM vs 93 nM for WT). In contrast, neither AP26113 nor crizotinib was active against the secondary ROS1 kinase domain mutation G2032R, which has been found in tumors that have progressed on crizotinib.

In Study # ARP205, the Applicant investigated the effects of AP26113 on in vitro signaling and growth in NSCLC cell lines expressing WT or mutant EGFR compared to the EGFR inhibitor erlotinib. NSCLC cell lines endogenously expressing WT EGFR (H358 cells), EGFR-Del (HCC827 cells), and L858R/T790M (H1975 cells) were used, along with HCC827 cells transduced with EGFR-Del/T790M. As assessed by western blotting, pre-treatment with erlotinib for 2 hours inhibited EGF-induced phosphorylation of endogenous WT EGFR at Tyr 1068 in H358 cells with an IC_{50} value of 65 nM, whereas AP26113 was much less effective (IC_{50} >3000 nM). Measured by ELISA, AP26113 inhibited phosphorylation of EGFR-Del, EGFR-Del/T790M, and EGFR-L858R/T790M with IC_{50} values ≤62 nM (see Table 5) while erlotinib inhibited phosphorylation of EGFR-Del (IC_{50} = 5 nM) but was ineffective against EGFR T790M mutations (IC_{50} >3000 nM). Consistent with these data, AP26113 inhibited phosphorylation of the downstream EGFR

signaling proteins AKT, SHC, and ERK in HCC827 cells expressing EGFR-Del and EGFR-Del/T790M, as well as AKT and ERK1/2 (but not STAT3) in H1975 cells expressing L858R/T790M. Further, as assessed using a CyQuant assay, incubation with AP26113 for 72 hours inhibited the in vitro growth of HCC827 cells expressing EGFR-Del and EGFR-Del/T790M (see Table 5 for IC_{50} values), whereas erlotinib was only effective against EGFR-Del (IC_{50} = 13 nM). These data suggest that AP26113 is selective for EGFR mutants tested compared to WT EGFR. The Applicant also assessed the in vitro activity of AP26113 against Ba/F3 cells stably transduced with EGFR mutations (Study # ARP624). As assessed using the MTS assay, incubation with AP26113 for 3 days inhibited the growth of Ba/F3 cells expressing 4 EGFR mutations with IC_{50} and IC_{90} values ≤489 nM and ≤2968 nM, respectively (see Table 5). As expected, erlotinib inhibited EGFR-Del (IC_{50} = 4.7 nM; IC_{90} = 29 nM) and L858R (IC_{50} = 13 nM; IC_{90} = 45 nM), but not variants containing T790M (IC_{50} ≥6688 nM; IC_{90} >10,000 nM). WT EGFR was not assessed in this study.

Table 5: Effect of Brigatinib on WT and Mutant EGFR in Kinase and Cellular In Vitro Assays

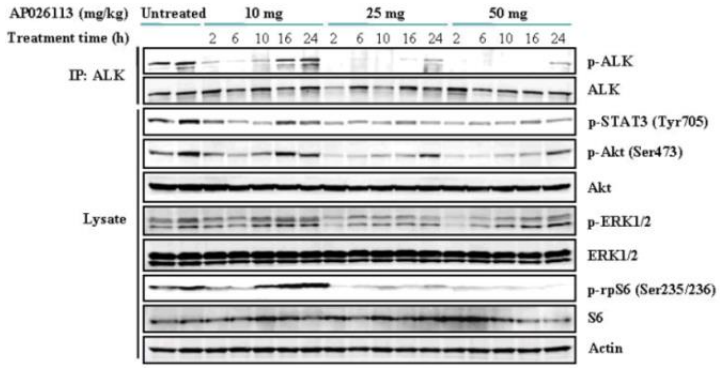
EGFR Variant	Kinase Screen[1]	Cell Line	ph-EGFR	Cell Growth		
	IC_{50} (nM)		IC_{50} (nM)[2]	GI_{50} (nM)[2]	IC_{50} (nM)[3]	IC_{90} (nM)[3]
WT	67	H358	>3000	ND	ND	ND
Del	ND	HCC827	62	163	ND	ND
		Ba/F3	ND	ND	95	314
Del/T790M	ND	HCC827	59	245	ND	ND
		Ba/F3	ND	ND	272	2461
L858R/T790M	29	H1975	47	ND	ND	ND
		Ba/F3	ND	ND	489	2968
L858R	1.5	Ba/F3	ND	ND	397	1201

(Reviewer generated table based on results from Study # ARP227[1], Study # ARP205[2], and Study # ARP624[3])

B. In Vivo Studies

The Applicant investigated the effect of single oral administration of 0, 10, 25, or 50 mg/kg AP26113 on downstream ALK signaling in EML4-ALK positive H3122 NSCLC cells implanted in female severe combined immunodeficient (SCID) (Study # ARP199). Immunoprecipitation and/or western blot analysis demonstrated that AP26113 inhibited in vivo phosphorylation of ALK (Tyr 1604), STAT3, AKT, ERK1/2, and S6 in tumor lysates in a time- and dose-dependent manner (see Figure 4). Inhibition occurred even at the low dose of 10 mg/kg (231 ng/mL C_{max}, 2246 ng*hr/mL AUC). Study # ARP615 demonstrated that daily oral administration of ≥10 mg/kg AP26113 for 4 days also induced dose-dependent inhibition of ALK phosphorylation in human KARPAS-299 ALCL tumors expressing NPM-ALK (data not shown).

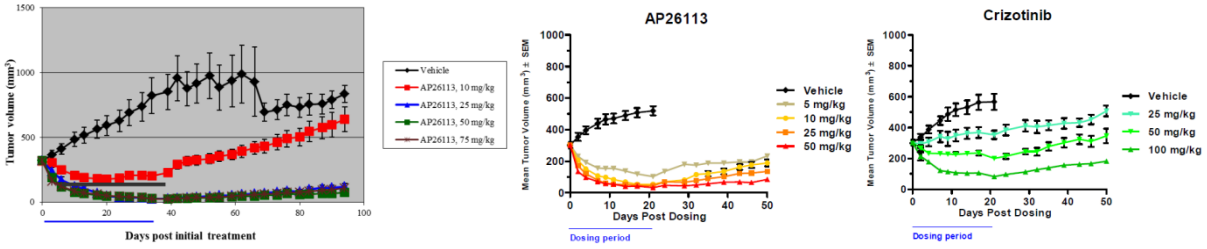
Figure 4: Effect of Brigatinib on Downstream ALK Signaling in H3122 NSCLC Xenografts



Representative western blot; (Applicant Figure reproduced from Study # ARP199)

The Applicant investigated the in vivo anti-tumor activity of AP26113 in 10 female SCID mice/group bearing established s.c. human NSCLC xenografts expressing EML4-ALK. Oral administration of AP26113 once daily at doses ≥5 mg/kg resulted in statistically significant dose-dependent regression of H3122 and H2228 xenografts without adverse clinical signs or mortality and mean body weight loss ≤12.5% (Study # ARP202 and # ARP616; see Figure 5). Higher doses of crizotinib were required to achieve comparable in vivo efficacy against H2228 xenografts.

Figure 5: Effect of Brigatinib on Human NSCLC EML4-ALK Xenograft Growth in SCID Mice



Left: H3122 cells; (Applicant Figure reproduced from Study # ARP202)
Middle and Right: H2228 cells; (Applicant Figures reproduced from Study # ARP616)

Once daily oral administration of ≥25 mg/kg AP26113 resulted in statistically significant regression of Ba/F3 xenografts engineered to express WT EML4-ALK or crizotinib-resistant ALK mutations L1196M (gatekeeper mutation), G1269S, S1206R, and G1202R s.c. implanted in 9-10 female SCID mice (Study # ARP215 and # ARP619) (Table 6) without clinical signs, significant body weight loss, or AP26113-related mortality. The G1202R ALK mutation has been associated with clinical resistance to crizotinib, ceritinib, and alectinib.

Table 6: Effect of Brigatinib on Growth of Ba/F3 Tumors Expressing WT or Mutant EML4-ALK

Drug	Dose	Tumor Growth Inhibition (TGI) or Tumor Regression (TR)					
		Study # ARP215; QD for 14 days				Study # ARP619; QD for 7 days	
		WT	L1196M	G1269S	S1206R	WT	G1202R
AP26113	10 mg/kg	22% TGI	ND	ND	ND	ND	ND
	25 mg/kg	100% TR**	52% TGI**	29% TR**	0% TGI	ND	55.1% TGI**
	50 mg/kg	100% TR**	59% TR**	98% TR**	29% TGI*	89.4% TR**	88.4% TGI**
	75 mg/kg	100% TR**	98% TR**	99.5% TR**	77% TGI**	ND	ND
Crizotinib	25 mg/kg	1% TGI	ND	ND	ND	ND	ND
	50 mg/kg	0% TGI	ND	ND	ND	ND	ND
	100 mg/kg	25% TGI	15% TGI	4% TGI	0% TGI	ND	23.4% TGI
	200 mg/kg	100% TR**	12% TGI	0% TGI	7% TGI	ND	45.8% TGI**
Alectinib	60 mg/kg	ND	ND	ND	ND	95.2% TR**	0.4% TGI
Ceritinib	50 mg/kg	ND	ND	ND	ND	97% TGI**	13.9% TGI

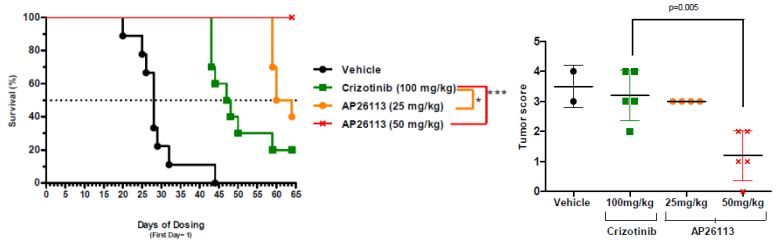
TGI = [(1- mean tumor volume change of treatment group) / mean tumor volume change of vehicle group] x 100
TR = (mean tumor volume change of treatment group / mean tumor volume at start of treatment) x 100
QD: once daily; ND: not determined; *, P < 0.05 vs. vehicle; **, P < 0.01 vs. vehicle
(Reviewer generated table based on results from Study # ARP215 and Study # ARP619)

Further, single oral administration of AP26113 reduced in vivo ALK phosphorylation in Ba/F3 xenografts expressing the ALK mutants L1196M, G1269S, and S1206R (≥25 mg/kg; Study # ARP229; data not shown) and G1202R [50 mg/kg (only dose tested); Study # ARP620; data not shown], indicating inhibition of in vivo ALK signaling.

Consistent with in vitro studies, AP26113 also exhibited dose-dependent in vivo anti-tumor activity against established s.c. Ba/F3 xenografts expressing CD74-ROS1 (Study # ARP623; data not shown). Once daily oral administration of ≥ 25 mg/kg AP26113 for 14 days resulted in tumor growth inhibition (TGI) ≥ 87% in female SCID mice without significant toxicity based on clinical signs, body weight loss, or mortality.

Daily oral administration of ≥25 mg/kg AP26113 to female SCID mice intracranially implanted with EML4-ALK expressing H2228 NSCLC cells significantly prolonged mouse survival compared to vehicle or 100 mg/kg crizotinib (Study # ARP621) (Figure 6). Mice dosed with AP26113 exhibited reduced body weight loss compared to vehicle-treated mice (data not shown). AP26113 was active in an in vivo NSCLC orthotopic brain tumor model, suggesting it may have activity against CNS metastases.

Figure 6: Effect of Brigatinib on Survival and Tumor Burden in a NSCLC Orthotopic Brain Tumor Model in SCID Mice



*, P = 0.03 vs. crizotinib; ***, P = 0.0002 vs. crizotinib; Tumor score evaluated based on visual quantitation of tumor area
(Applicant Figure reproduced from Study # ARP621)

Secondary Pharmacology

The Applicant investigated the ability of AP26113 to inhibit additional kinases in in vitro cellular assays (Study # ARP200 and # ARP629). As shown in Table 7, AP26113 inhibited IGF-1R, FLT3, and the secondary FLT3 mutations F691L and D835Y at clinically relevant concentrations in cellular assays, but exhibited minimal in vitro activity against InsR, RET, two RET secondary mutations, and six HER2 exon 20 mutants. WT HER2 was not tested in the MTS viability assay because it was unable to drive IL-3-independent growth of Ba/F3 cells. AP26113 was more potent in the in vitro kinase screen than in in vitro cellular assays for all kinases tested.

Table 7: In Vitro Effect of Brigatinib on IGF-1R, InsR, FLT3, RET, and HER2

	Kinase Screen[1]	Cellular Assay			
Kinase	**IC_{50} (nM)**	**Cell line**	**Method**	**IC_{50} (nM)**	**IC_{90} (nM)**
IGF-1R[a]	73	HepG2	ELISA/western blot[2]	148.3	ND
InsR[b]	160	H-4-II-E	ELISA/western blot[2]	9331	ND
FLT3	2.1	Ba/F3	MTS viability[3]	158	465
F691I	ND			1155	2392
F691L	ND			263	576
D835Y	1.5			211	638
RET	65	Ba/F3	MTS viability[3]	1412	5477
V804L	27			681	1556
V804M	22			975	3125
HER2 exon 20 mutants	ND	Ba/F3	MTS viability[3]	1410-4565	ND

ND: not determined; [a]: IGF-1-induced IGF-1R phosphorylation; [b]: insulin-induced InsR phosphorylation
(Reviewer generated table based on results from Study # ARP227[1], Study # ARP200[2], and Study # ARP629[3])

The off-target activity of AP26113 on 62 receptors, ion channels, steroids, peptides, and transporters was evaluated in Study # ARP630 using in vitro receptor binding and enzyme assays. Incubation with 10 µM AP26113 inhibited 2/62 targets (3%) by ≥50%: the non-selective sigma receptor (79% inhibition) and the sodium ion channel (site 2; 91% inhibition). The Applicant investigated neither the functional consequences of inhibiting these targets nor inhibition at lower concentrations.

Safety Pharmacology

In non-GLP Study # AA778105, HEK293 cells stably expressing the human hERG potassium channel were incubated with brigatinib (0.1, 1, and 10 µM), 0.1% DMSO (negative control), or 10 µM cisapride (positive control) followed by measurement of potassium current using the patch-clamp technique. Negative and positive controls behaved as expected. AP26113 inhibited the hERG potassium current with an IC_{50} value >10 µM (n=3), suggesting minimal risk of QT prolongation in humans given brigatinib.

In order to assess the effects of AP26113 on the cardiovascular and respiratory systems, radiotelemetry-instrumented male cynomolgus monkeys were administered a single oral dose of AP26113 at 0, 10, 20, and 30 mg/kg using a latin square cross-over design with a 4 day washout period between doses; heart rate, arterial blood pressure, pulse pressure, body temperature, ECG parameters (PR, QRS, QT, and QTcB), respiratory frequency, tidal volume, and minute volume were measured continuously for approximately 3 hours pre-dosing and 48 hours post-dosing (Study # (b) (4)-69507; GLP-compliant). Following the cardiorespiratory phase, three of these monkeys were dosed again with 10, 20, and 30 mg/kg AP26113 with 4 days between doses and blood was collected pre-dosing and at 0.5, 1, 2, 4, 8, 12, 24, and 48 hours post-dose for pharmacokinetic (PK) analysis. Consistent with the in vitro hERG data, treatment with AP26113 at dose levels up to 30 mg/kg did not result in QT or QTcB prolongation in monkeys. Single oral administration of AP26113 resulted in a decrease in mean pulse pressure and heart rate 1-6 hours post-dose compared to controls at clinically relevant exposures, correlating with bradycardia observed in humans given brigatinib (Table 8). Delayed effects on cardiopulmonary function included elevated heart rate, blood pressure, body temperature (≤2 increase at 30 mg/kg after 32 hours), and respiratory frequency (up to 33% increase at 30 mg/kg after 33 hours) compared to controls; these effects were generally seen at AP26113 exposures within ~0.6- to 2-fold of those achieved clinically at the 180 mg dose level. Hypertension and pulmonary toxicity have been observed clinically with brigatinib.

Table 8: Effect of Single Oral Administration of Brigatinib on Hemodynamic Parameters in Monkeys Compared to Controls

	Heart rate			Systolic BP			Diastolic BP			MAP			Pulse Pressure		
Dose (mg/kg)	**10**	**20**	**30**	**10**	**20**	**30**	**10**	**20**	**30**	**10**	**20**	**30**	**10**	**20**	**30**
1-6 hr	8%↓	10%↓	9%↓											9%↓	8%↓
32 hr			21%↑			15%↑			14%↑						
33-42 hr		11%↑	23%↑	6%↑	5%↑	9%↑						7%↑			

All percent changes listed in table are statistically significant (P < 0.05) compared to control; BP: blood pressure; MAP: mean arterial pressure
(Reviewer generated table based on results from Study # (b) (4) 69507)

In GLP-compliant Study # 6900915, 8 male Sprague-Dawley rats/group were administered a single oral dose of AP26113 at 0, 25, 50, or 100 mg/kg; functional observation battery (FOB) tests were performed pre-dosing and 4, 8, and 24 hours post-dose to evaluate the effects of

AP26113 on the CNS. FOB tests included 25 qualitative assessments (e.g. posture, convulsions, rearing, pupillary response, gait, body tone, grooming, piloerection, tail pinch, reflexes), grip strength, hind limb splay, and rectal body temperature. There was an increase in the incidence of ptosis at 8 hours after administration of ≥50 mg/kg AP26113 compared to controls, although there was no clear dose response at 24 hours. Single oral administration of AP26113 at dose levels up to 100 mg/kg did not adversely affect any other CNS parameters.

Table 9: Effect of Single Oral Administration of Brigatinib on CNS Function in Rats

Dose (mg/kg)	0	25	50	100
Ptosis: 8 hrs		1	2	2
24 hrs	1	1	3	1
Forelimb grip strength: 4 hrs		8%↑	8%↑	13%↑
8 hrs		12%↑	16%↑	19%↑*
24 hrs		17%↑	21%↑*	15%↑
Hindlimb grip strength: 4 hrs		14%↑	8%↑	22%↑
8 hrs		20%↑	5%↑	29%↑**
24 hrs		14%↑	8%↑	25%↑
Body temperature: 24 hrs				1%↓*

Ptosis data shown as rat incidence; % compared to controls; *, P < 0.05; **, P < 0.01
(Reviewer generated table based on results from Study # 6900915)

In GLP-compliant Study # 6900893, 8 male Sprague-Dawley rats/group were administered a single oral dose of AP26113 at 0, 25, 50, or 100 mg/kg; clinical chemistry, urinalysis, and urine chemistry parameters were measured at 10 and 24 hours post-dose to evaluate the effects of AP26113 on the renal system. Single oral administration of AP26113 resulted in elevated urea nitrogen, creatinine, glucose, creatine kinase, calcium, urine volume, and fractional phosphorus/sodium/potassium/chloride excretion in the urine compared to controls, as well as decreased phosphorous, sodium, chloride, urine creatinine, and creatinine clearance compared to controls. These findings are indicative of renal toxicity and suggest that AP26113 may impair renal function at dose levels ≥25 mg/kg.

Table 10: Effect of Single Oral Administration of Brigatinib on Renal Parameters

Parameters	Major findings compared to controls
Clinical Chemistry	Dose-dependent increase in urea nitrogen up to 73% (10 hr PD) at HD; ≤45% increase at 24 hrs PD. Dose-dependent increase in glucose up to 134% (10 hr PD) and 352% (24 hr PD) at HD. Dose-dependent increase in creatinine up to 62% (24 hr PD) at HD. Statistically significant increase in creatine kinase (≥50 mg/kg), calcium (≥25 mg/kg), and globulin (≥25 mg/kg) at 24 hr PD. Statistically significant decrease in triglycerides (≥25 mg/kg), phosphorus (≥50 mg/kg; 10 hr PD only), sodium (≥50 mg/kg), and chloride (≥25 mg/kg) at 10 and 24 hr PD.
Urinalysis	Dose-dependent increase in specific gravity up to 2% (24 hr PD) at HD. Dose-dependent increase in fractional phosphorous excretion up to 454% (10 hr PD) and 137% (24 hr PD) at HD. Statistically significant increase in urine volume (≥50 mg/kg; 10 hr PD), fractional sodium excretion (50 mg/kg, 24 hr PD; 100 mg/kg 10 hr PD), fractional potassium excretion (≥25 mg/kg; 24 hr PD), and fractional chloride excretion (≥25 mg/kg; 24 hr PD). Statistically significant decrease in urine creatinine (≥25 mg/kg; 10 hr PD) and creatinine clearance (≥25 mg/kg; 24 hr PD).

HD: high dose; PD: post-dose; (Reviewer generated table based on results from Study # 6900893)

5.4. ADME/PK

Type of Study	Major Findings
Distribution	
In Vitro Plasma Protein Binding and Equilibrium Blood/Plasma Partitioning of AP26113 in Mouse, Rat, Monkey and Human. ARIAD Report No. ARP210	AP26113 was moderately bound (64-73%) to plasma proteins in mouse, rat, monkey, and human plasma proteins.
Metabolism	
In Vitro Biotransformation of [^{14}C]Brigatinib in Liver Microsomes and Hepatocytes of Mouse, Rat, Monkey and Human, and in Recombinant Human CYP Isozymes. Study Report No. ARP608.	AP26113 was metabolized almost exclusively by CYP2C8 and CYP3A4 (contributions of 72.4% and 27.6%, respectively). Metabolism of AP26113 in rat and monkey liver microsomes and hepatocytes was qualitatively similar to that in human liver microsomes and hepatocytes. All in vitro human metabolites of brigatinib in human liver microsomes and hepatocytes were also present in mouse, rat or monkey liver microsomes and/or hepatocytes. No unique human metabolites were detected.
Excretion	
Mass Balance and Metabolism of [^{14}C]Brigatinib in Male Cynomolgus Monkeys Following a Single Oral Dose: Metabolite Profiling and Characterization. Study Report No. ARP610	After oral administration of [^{14}C]brigatinib to monkeys, the majority of the radioactivity (66.48 ± 6.46%) was excreted in feces, and urine accounted for 9.75 ± 0.87% of the administered dose, similar to rats.
PK-Drug Interaction	
Evaluate the Substrate and Inhibition Potential of AP26113 for Efflux and Uptake Transporters. Absorption Systems Study Number 13ARIAP1R2	AP26113 is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but not a substrate of organic anion transporting polypeptides 1B1 and 1B3 (OATP1B1,OATP1B3), organic anion transporters 1 and 3 (OAT1, OAT3), organic cation transporters 1 and 2 (OCT1, OCT2), multidrug and toxin extrusion proteins 1 and 2K (MATE1, MATE2K), or bile salt export pump (BSEP).
In Vitro Evaluation of AP26113 as an Inhibitor of Human Cytochrome P450 Enzymes. ARIAD Report No. ARP212	AP26123 was not a metabolism dependent (MDI) or a time-dependent inhibitor (TDI) of seven CYP isoforms evaluated (CYP1A2, CYP2B6, CYP2C9, CYP2C8, CYP2C19, CYP2D6, CYP3A4/5). Therefore, drug-drug interactions (DDI) due to inhibition of CYPs by AP26113 or its metabolite AP26123 are unlikely.
In Vitro Evaluation of AP26113 as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes. (b) (4) Study Number: (b) (4) 123144	Treatment of cultured human hepatocytes with up to 20 µM AP26113 did not induce the expression of cytochrome P450 enzymes (CYP1A2, CYP2B6 or CYP3A4/5 activity (< 2-fold change or < 20% of the positive control) or CYP1A2 or CYP2B6 mRNA levels). Treatment of human hepatocyte cultures with the positive control CYP inducers caused anticipated and appropriate increases in CYP activity and mRNA levels

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>TK data from general toxicology studies</td><td></td></tr>
<tr><td>A 6-Month Oral Gavage Toxicity Study of AP26113 in Sprague Dawley Rats with a 56-Day Recovery Period.
Study Number (b) (4)-69505.</td><td>T1/2 could not be estimated
No accumulation
In rats, exposure was dose proportional between 7.5 and 15 mg/kg/day and less than dose proportional between 15 and 25 mg/kg/day. No apparent differences in exposure between males and females.

<table>
<tr><th rowspan="2">Day</th><th rowspan="2">Dose Mg/kg/day</th><th colspan="2">Cmax (ng/mL)</th><th colspan="2">AUC(0-t) (hr.ng/mL)-</th></tr>
<tr><th>Male</th><th>Female</th><th>Male</th><th>Female</th></tr>
<tr><td>0</td><td>7.5</td><td>1010</td><td>1030</td><td>12200</td><td>12100</td></tr>
<tr><td></td><td>15</td><td>1970</td><td>1490</td><td>23800</td><td>21600</td></tr>
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<tr><td></td><td>15</td><td>2020</td><td>1850</td><td>37600</td><td>32700</td></tr>
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<tr><td>A 6-Month Oral (Nasogastric) Toxicity and Toxicokinetic Study of AP26113 in Cynomolgus Monkeys with a 56-Day Recovery Period.
Study Number (b) (4)-69506.</td><td>
<table>
<tr><th rowspan="2">Day</th><th rowspan="2">Dose (mg/kg/day)</th><th colspan="2">Cmax (ng/mL)</th><th colspan="2">AUC (0-t)(hr.ng/mL</th></tr>
<tr><th>Male</th><th>Female</th><th>Male</th><th>Female</th></tr>
<tr><td>0</td><td>5</td><td>248</td><td>555</td><td>2060</td><td>3140</td></tr>
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<tr><td>TK data from reproductive toxicology studies</td><td></td></tr>
<tr><td>An Embryo-fetal Development Study of AP26113 by Oral Gavage in Rats. (b) (4) Study No. 9000674</td><td>
<table>
<tr><th>Day</th><th>Dose (mg/kg)</th><th>Cmax (ng/mL)</th><th>Cmax/D (ng/mL(mg/kg))</th><th>AUC (0-t) (hr*ng/mL)</th></tr>
<tr><td>6</td><td>5</td><td>791</td><td>158</td><td>9650</td></tr>
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<tr><td></td><td>25</td><td>1530</td><td>61.3</td><td>25500</td></tr>
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</table>

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: A 6-Month Oral Gavage Toxicity Study of AP26113 in Sprague Dawley Rats with a 56-Day Recovery Period /Study Number (b) (4)-69505.

Key Study Findings

- Oral gavage administration of AP26113 to rats caused mortalities in a dose-dependent manner at doses ≥15 mg/kg (total of 19 unscheduled deaths); early termination of dosing for surviving 25 mg/kg high dose group after Day 53
- Ophthalmic toxicological effects included cataract (bilateral) and retinal degeneration in a dose and time dependent manner.
- Dose-related microscopic findings in the kidneys, liver, heart, pancreas, spleen, thymus, testes, and epididymis.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	7.5, 15, and 25 mg/kg/day Once daily for 184 consecutive days to toxicology groups and for up to 183 consecutive days to toxicokinetic groups
Route of administration:	Oral gavage
Formulation/Vehicle:	25 mM citrate buffer, pH 4.0 ± 0.1
Species/Strain:	Crl:CD (SD) rats
Number/Sex/Group:	Main: 25/sex/group Recovery: 10/sex/group
Age:	Approximately 51 days
Satellite groups/ unique design:	Yes, toxicokinetic animals
Deviation from study protocol affecting interpretation of results:	None

Observations and Results: changes from control

Parameters	Major findings
Mortality	Control – 1 M died or euthanized prior to primary necropsy; accidental death 7.5 mg/kg/day – 2 M + 1 F died or euthanized prior to primary necropsy (study Days 87-167); cause of death in these animals considered incidental (sepsis, possible gavage injury) 15 mg/kg/day – 5 M + 4 F died or euthanized prior to primary necropsy (study Days 76-183). Acute cardiac lesions were the cause of death in 2 of the 9 unscheduled deaths. Chronic renal lesions were the

<table>
<tr><td></td><td>cause of death in 6 animals
25 mg/kg/day – 4 M + 2F died between study Days 35 and 49
15 M + 15 F euthanized following 53 days of dose administration. Test article-related acute cardiac lesions were the cause of deaths. Remaining 6 M + 8 F not dosed from study day 53 onwards and euthanized following a 56-day non-dosing (recovery) period.
A total of 19 unscheduled deaths</td></tr>
<tr><td>Clinical Signs</td><td>7.5 mg/kg/day – dried/wet material around the nose and mouth
15 mg/kg/day – hypoactivity, tonic convulsions, impaired equilibrium, thin, dermal atonia, thin, labored respiration, decreased defecation, red urine, brown material around the mouth, nose, and anogenital area.
25 mg/kg/day – pale and/or cool body, extremities, dermal atonia, thin, increased respiration rate, decreased defecation, dried brown/red material around the nose, mouth and/or anogenital area.</td></tr>
<tr><td>Body Weights</td><td>Week 7
MD - Males (↓16%), Females (↓10%) vs. control
HD - Males (↓32%), Females (↓18%)
Week 26
LD – Males (↓14%), Females (↓5%) vs. control
MD - Males (↓29), Females (↓20%)

Changes reflect decreased body weight gain compared to controls; No effect on food consumption noted</td></tr>
<tr><td>Ophthalmoscopy</td><td>Dose and duration-related cataracts and retinal degeneration

<table>
<tr><td rowspan="3">Group</td><td colspan="4">Cataract</td><td colspan="4">Retinal Degeneration</td></tr>
<tr><td colspan="2">Male</td><td colspan="2">Female</td><td colspan="2">Male</td><td colspan="2">Female</td></tr>
<tr><td>Week 25</td><td>Week 33</td><td>Week 25</td><td>Week 33</td><td>Week 25</td><td>Week 33</td><td>Week 25</td><td>Week 33</td></tr>
<tr><td>1</td><td>0/24</td><td>0/9</td><td>0/25</td><td>0/10</td><td>0/24</td><td>0/9</td><td>0/25</td><td>0/10</td></tr>
<tr><td>2</td><td>1/23</td><td>1/10</td><td>0/24</td><td>2/9</td><td>0/23</td><td>0/10</td><td>0/24</td><td>0/9</td></tr>
<tr><td>3</td><td>3/20</td><td>4/8</td><td>0/23</td><td>1/8</td><td>0/20</td><td>0/8</td><td>3/23</td><td>1/8</td></tr>
<tr><td>4</td><td colspan="8">Terminated early – not examined</td></tr>
</table></td></tr>
<tr><td>Hematology</td><td>Week 26
LD – platelet (↑17%), WBC (↓15%), lymph absolute (↓22%)
MD – platelet (↑40%), WBC (↓30%), lymph absolute (↓59%)
HD –Not applicable - due to high mortality, surviving animals were not dosed after Day 53</td></tr>
<tr><td>Clinical Chemistry</td><td>Week 26-Percent Differences in Mean Values vs. Concurrent Controls
<table>
<tr><td>Sex</td><td colspan="2">Males</td><td colspan="2">Females</td></tr>
<tr><td>Group</td><td>LD</td><td>MD</td><td>LD</td><td>MD</td></tr>
<tr><td>Dose (mg/kg)</td><td>7.5</td><td>15</td><td>7.5</td><td>15</td></tr>
<tr><td>ALP (↑)</td><td>48</td><td>103</td><td>-</td><td>220</td></tr>
<tr><td>ALT (↑)</td><td>160</td><td>1176</td><td>-</td><td>583</td></tr>
<tr><td>AST (↑)</td><td>109</td><td>1121</td><td>-</td><td>847</td></tr>
<tr><td>Cholesterol (↑)</td><td>-</td><td>64</td><td>-</td><td>95</td></tr>
<tr><td>Urea nitrogen (↑)</td><td>-</td><td>36</td><td>-</td><td>150</td></tr>
<tr><td>Creatinine (↑)</td><td>-</td><td>28</td><td>-</td><td>103</td></tr>
<tr><td>Glucose (↑)</td><td>17</td><td>18</td><td>-</td><td>18</td></tr>
</table></td></tr>
<tr><td>Urinalysis</td><td>Week 26-Percent Differences in Mean Values vs. concurrent Controls</td></tr>
</table>

<table>
<tr><td></td><td>Excretion
<table>
<tr><td>Sex</td><td colspan="2">Males</td><td colspan="2">Females</td></tr>
<tr><td>Group</td><td>LD</td><td>MD</td><td>LD</td><td>MD</td></tr>
<tr><td>Dose (mg/kg)</td><td>7.5</td><td>15</td><td>7.5</td><td>15</td></tr>
<tr><td>Potassium</td><td>56</td><td>116</td><td>-</td><td>164</td></tr>
<tr><td>Chloride</td><td>-</td><td>236</td><td>0</td><td>314</td></tr>
</table></td></tr>
<tr><td>Gross Pathology</td><td>Test article-related gross observations were noted in the kidneys, thymus, liver, and testes.</td></tr>
<tr><td>Organ Weights</td><td>Lower weights of thymus, spleen, pituitary gland, testes, seminal vesicles/prostate, and epididymis as compared to controls were noted.</td></tr>
<tr><td>Histopathology
Adequate battery:</td><td>Yes
Drug-related histopathology findings were seen in the following organs:
Heart: myocardial degeneration, cardiomyopathy, and hemorrhage
Kidneys: tubular dilation/necrosis, glomerulonephritis,
Liver: necrosis
Lymphatic system: necrosis and reduced cellularity
Pancreas: acinar atrophy and islet fibroplasia
Epididymis: cellular debris and sperm count reduction
Testes: tubular degeneration
See Table 11 and Table 12 for detailed findings in the unscheduled death and main sacrifice groups after 26 weeks (LD and MD). See Appendix for findings following 7 weeks post dosing for HD group and recovery sacrifices.</td></tr>
<tr><td colspan="2">Recovery:
New findings in the 34-week recovery animals that were not detected in the main sacrifice: hemorrhage and phthisis bulbi in one mid-dose female; presence of proestrus cycle in 2 low-dose and one high-dose females.
Reduced sperm was persistent through the end of the 34-week recovery.
Other findings were reversible.</td></tr>
</table>

NA: Not applicable; LD: low dose; MD: mid dose; HD: high dose.

Table 11: Histopathological Findings (Rat) Unscheduled Deaths-Selected Organs

Sex	Male				Female			
Dose (mg/kg)	0	7.5	15	25	0	7.5	15	25
Findings Number of Animal Examined	1	2	5	4	0	1	4	2
Heart, cardiomyopathy, minimal	-	-	-	-	-	-	1	-
mild	-	1	-	-				
moderate	-	-	-	1				
Degeneration, myocardial, minimal	-	-	-	1				
mild	-	-	3	-	-	1	2	2
moderate	-	-	2	2				
severe	-	-	-	1				
Hemorrhage, acute, minimal	-	-	1	-				
mild	-	-	2	-				
moderate	-	-	-	3				
Infiltrate, mononuclear cell, minimal	-	-	1	-				
Pigment, brown, minimal	-	-	1	-				
Kidneys, accumulation, pigment, mild	-	-	3	-	-	-	1	-

Sex	Male				Female			
Dose (mg/kg)	0	7.5	15	25	0	7.5	15	25
Findings Number of Animal Examined	1	2	5	4	0	1	4	2
moderate	-	-	1	-	-	-	2	-
Basophilia, tubule, minimal	-	1	-	4	-	-	-	2
mild	-	-	2	-				
moderate	-	-	1	-				
Dilation, tubular, mild	-	-	1	1				
moderate	-	-	2	2	-	-	-	2
severe	-	-	2	1	-	-	4	-
Glomerulonephritis, mild	-	-	2	2				
moderate	-	-	3	2	-	-	4	1
Necrosis, tubular, mild					-	-	1	1
Pancreas, atrophy, acinar, minimal					-	-	1	-
Mild					-	-	2	2
Moderate	-	-	1	1	-	-	2	2
Fibroplasia, islets, moderate	-	1	-	4	-	-	-	2
Hemorrhage, acute, mild	-	-	-	2				

Note: Findings in organs not listed are comparable to those in main necropsy.

Table 12: Histopathological Findings (Rat) Week 26 Primary Necropsy

Sex	Males			Females		
Dosage (mg/kg/day)	0	7.5	15	0	7.5	15
Findings Number of Animal Examined	15	13	12	15	15	13
Epididymis, cellular debris, minimal	-	-	3			
mild	-	1	3			
Reduced sperm, luminal, minimal	-	-	2			
Heart, degeneration, myocardial, minimal	2	1	-	-	-	1
mild	-	-	-	-	-	1
Kidneys, dilation, tubular, minimal	-	1	5	-	2	2
mild	-	1	3	-	1	7
moderate	-	-	1	-	1	2
Accumulation, pigment, minimal	-	6	2	0	7	-
mild	-	6	7	-	8	6
moderate-	-	1	3	-	-	7
Liver, necrosis, minimal	-	2	1	-	-	1
mild	-	2	4	-	-	2
moderate	-	-	4	-	-	2
LN, Axillary, reduced cellularity, mild	-	8	1	1	2	4
moderate	-	-	-	-	-	1
LN, Mesenteric, reduced cellularity, mild	-	-	1	-	-	4
moderate	-	-	-	-	-	1
Pancreas, islet fibroplasia, minimal	-	3	4	-	-	1
mild	1	2	2	-	-	1
moderate	-	-	3	-	-	-
Atrophy, acinar, minimal	-	1	2	-	-	-
Mild	1	3	2	-	1	2
Spleen. reduced cellularity, mild	-	2	3	-	2	1

Sex		Males			Females		
Dosage (mg/kg/day)		0	7.5	15	0	7.5	15
Findings	Number of Animal Examined	15	13	12	15	15	13
Pigment, brown, minimal	moderate	-	-	-	-	-	1
	minimal	-	-	-	2	1	-
	mild	1	6	1	7	8	3
	moderate	-	2	5	-	4	5
Testes, degeneration, minimal		-	3	3			
	Moderate	-	1	3			
Thymus, reduced cellularity, mild		1	5	7	1	6	8
	moderate	-	-	2	-	1	5

Study title/ number:
A 6-Month Oral (Nasogastric) Toxicity and Toxicokinetic Study of AP26113 in Cynomolgus Monkeys with a 56-Day Recovery Period. Study Number: (b) (4)-69506.

Key Study Findings

- Oral administration of AP26113 at 15 mg/kg/day resulted in moribundity in male monkeys due inflammation of the lungs and pericardium.
- There were no dose-related effects on heart rate, RR interval, PR interval, QRS duration, QT interval or QTC interval at approximately 4 hours post-dose.
- Test article related microscopic findings were seen in the kidneys, lymphoid organs, lungs, spleen, and thymus. No clear correlates with clinical chemistry were observed; slight decreases in lymphocytes and total WBCs.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	5, 10, and 15 mg/kg/day, once daily for 6 consecutive months with 56-day recovery period
Route of administration:	Oral (nasogastric intubation)
Formulation/Vehicle:	25 mM citrate buffer, pH 4 ± 0.1
Species/Strain:	Cynomolgus monkeys (Macaca fascicularis)
Number/Sex/Group:	5
Age:	3-4years
Satellite groups/ unique design:	No
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

<table>
<tr><th>Parameters</th><th>Major findings</th></tr>
<tr><td>Mortality (twice daily)</td><td>LD – 1 male died on Day 106 due to leg injury
HD – 2 males died (on Days 12 and 53) and 2 males euthanized on Day 62. The cause of death was attributed to the inflammation of the lungs and pericardium.</td></tr>
<tr><td>Clinical Signs (daily)</td><td>HD –Hypoactivity, hunched posture, pale/cool body, pale extremities, shallow respiration, partial closure eyes</td></tr>
<tr><td>Body Weights (weekly)</td><td>No clear dose-related effect</td></tr>
<tr><td>Ophthalmoscopy (Weeks -2, 8 and 25)</td><td>No ophthalmic lesions due to test-article</td></tr>
<tr><td>Hematology (Weeks 8, 12, 16, 26 {primary necropsy}, and 34 [recovery necropsy])</td><td>LD – No effect
MD - 39% ↓ WBC in Males, 50% ↓ Lymph absolute in M & F, 39% ↓ absolute reticulocyte count in Males vs control animals on Week 26
HD – 50% ↓ lymph absolute in females. Males not reported</td></tr>
<tr><td>ECG (Weeks -3, 8, 12, and 25)</td><td>No dose-related effect at approximately 4 hours post-dose</td></tr>
<tr><td>Clinical Chemistry</td><td>No test article-related alterations</td></tr>
<tr><td>Urinalysis</td><td>No alterations</td></tr>
<tr><td>Gross Pathology</td><td>Small thymus and dark red discoloration of the kidneys</td></tr>
<tr><td>Organ Weights</td><td>Test article-related lower spleen, testes, pituitary gland, and thymus were noted in the 5, 10, and/or 15 mg/kg/day group animals.</td></tr>
<tr><td>Histopathology
Adequate battery: Yes</td><td>Histopathological Findings, Primary Necropsy
<table>
<tr><td>Sex</td><td colspan="2">Males</td><td colspan="3">Females</td></tr>
<tr><td>Tissue Dose (mg/kg/day)</td><td>5</td><td>10</td><td>5</td><td>10</td><td>15</td></tr>
<tr><td>Kidneys, accumulation, pigment, minimal</td><td>1</td><td>1</td><td>3</td><td>1</td><td>-</td></tr>
<tr><td>mild</td><td>2</td><td>2</td><td>-</td><td>2</td><td>2</td></tr>
<tr><td>moderate</td><td>-</td><td>-</td><td>-</td><td>-</td><td>1</td></tr>
<tr><td>Lungs, macrophages, alveolar, minimal-</td><td>-</td><td>-</td><td>-</td><td>2</td><td>-</td></tr>
<tr><td>mild-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>2</td></tr>
<tr><td>Lymph node, axillary, reduced cellularity, minimal</td><td>-</td><td>1</td><td>1</td><td>1</td><td>-</td></tr>
<tr><td>mild</td><td>1</td><td>1</td><td>1</td><td>2</td><td>3</td></tr>
<tr><td>Prostate, immaturity, present</td><td>1</td><td>0</td><td></td><td></td><td></td></tr>
<tr><td>Seminal vesicles, immaturity, present</td><td>1</td><td>0</td><td></td><td></td><td></td></tr>
<tr><td>Mineralization, mild</td><td>0</td><td>1</td><td></td><td></td><td></td></tr>
<tr><td>moderate</td><td>1</td><td>0</td><td></td><td></td><td></td></tr>
<tr><td>Spleen, contracted, present</td><td>-</td><td>1</td><td>-</td><td>2</td><td>1</td></tr>
<tr><td>Testes, degeneration, tubular, minimal</td><td>1</td><td>0</td><td></td><td></td><td></td></tr>
<tr><td>Immaturity present</td><td>1</td><td>0</td><td></td><td></td><td></td></tr>
<tr><td>Thymus, reduced cellularity, mild</td><td>1</td><td>1</td><td>-</td><td>1</td><td>1</td></tr>
<tr><td>Moderate</td><td>1</td><td>1</td><td>-</td><td>1</td><td>2</td></tr>
</table></td></tr>
<tr><td>Insulin and Glucose</td><td>No dose-related effects</td></tr>
</table>

General toxicology; additional studies

One month toxicology studies were conducted in rats and monkeys. Adverse findings were generally similar to those reported in the 6 month studies.

5.5.2. Genetic Toxicology

Study title/ number: Bacterial Reverse Mutation Test in Salmonella Typhimurium and Escherichia Coli / (b) (4) Study No. 9600382.

Key Study Findings:

- AP26113 up to 5000 ug/plate did not show genotoxic activity in Salmonella typhimurium strains (TA1535, TA1537, TA98, TA100) and Escherichia coli strain WP2uvrA in the presence and absence of S9 mix.
- Standard positive controls confirm the sensitivity and validity of the assay.

GLP compliance: Yes
Test system: Salmonella strains TA1535, TA1537, TA98, TA100 and E.coli Wp2uvrA; up to 5000 ug/plate; +/- S9
Study is valid: Yes

Study title/ number: In Vitro Mammalian Chromosome Aberration Test in Human Peripheral Blood Lymphocytes / (b) (4) Study No. 9600383

Key Study Findings:

- AP26113 did not show any evidence of genotoxic activity in the in vitro mammalian chromosome aberration test in the absence or presence of S9 mix.
- The positive controls caused substantial increases in the proportion of aberrant metaphases in each phase of the study, confirming the sensitivity and validity of the test system.

GLP compliance: Yes
Test system: human peripheral blood lymphocytes; up to 500 ug/mL; +/-S9
Study is valid: Yes

Study title/ number: Mammalian Erythrocyte Micronucleus Test in Rat Bone Marrow / (b) (4) Study Number 9800314.

Key Study Findings:

- Oral administration of AP26113 at ≤ 50 mg/kg/day (10, 25, and 50 mg/kg/day) for 2 days, showed evidence of dose-dependent chromosomal damage; induction of < 2-fold compared to vehicle control.
- AP26113 at 125 mg/kg/day (MTD) showed chromosomal damage > 2-fold (clastogenic effects) compared to vehicle control.

GLP compliance: Yes

Test system: rat, bone marrow micronuclei; two oral doses of 10, 25, 50, 125, and 150 mg/kg/day administered 24 hours apart
Positive control – 20 mg/kg cyclophosphamide
Study is valid: Yes

Table 13: Brigatinib In Vivo Micronucleus Assay Results

Group	Dose (mg/g/day)	% IE/(IE+ME)	% MIE	% MME	P-Value
1	vehicle control	58.3	0.200	0.00	
2	10	55.9	0.140	0.00	0.9430
3	25	44.5	0.285	0.00	0.0517
4	50	40.6	0.340	0.05	0.0045
5	Positive control	47.1	3.533	0.00	<0.0001
6	125	42.3	0.410	0.00	<0.0001

%IE/(IE+ME) - Proportion of immature erythrocytes
%MIE - Percentage of micronucleated immature erythrocytes
%MME - Percentage of micronucleated mature erythrocytes
P-Value - One-Sided Fisher's Exact Test P-Value

Other Genetic Toxicity Studies: None

5.5.3. Carcinogenicity

None submitted or required for the proposed indication.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Neither submitted nor required

Embryo-Fetal Development

Study title/ number: An Embryo-fetal Development Study of AP26113 by Oral Gavage in Rats / Test Facility Study No. 9000674

Key Study Findings

- Oral gavage administration of AP26113 at 5, 12.5, and 25 mg/kg/day to pregnant rats on Days 6 to 17 post coitum did not cause any maternal mortality but at the high dose there was a 24% reduction in body weight and two dams had total resorption.
- There was a dose dependent decrease in litter fetal weights at doses ≥ 12.5 mg/kg/day.

- Treatment related external, visceral, and skeletal malformations were noted in 26 fetuses from 13 out of 20 high dose litters.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 5, 12.5, and 25 mg/kg/day
Daily from Days 6 t0 17 post coitum

Route of administration: Oral gavage

Formulation/Vehicle: 25 mM sodium citrate buffer pH 4.0

Species/Strain: Sprague Dawley CD (Crl:CD[SD] female rats, pregnant

Number/Sex/Group: 20

Satellite groups: Yes, 6 animals/group for toxicokinetics

Study design: Time-mated rats were treated once daily oral gavage from Days 6 to 17 post coitum

Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	**Major findings**
Mortality	None
Clinical Signs	LD: No effect MD: No effect HD: Vaginal discharge
Body Weights	LD: No effect MD: Slightly lower body weight during Day 6 to 9 pc only HD: Lower maternal body weight (~24% vs. control)
Necropsy findings Cesarean Section Data	LD: No effect MD: No effects on corpora lutea, implantation sites, live and dead fetuses and resorption, and pre implantation losses as compared to control values. Decreased litter mean fetal weight HD: 2 dams had total resorption, post implantation loss and resorption, decreased live fetuses, and decreased litter mean fetal weight
Necropsy findings	LD: No effect

Offspring	MD: Malformation: small tongue and/or hind limb hyperflexion (3 fetuses from 2 litters), Skeletal variation: incomplete ossification was noted in the parietal, interparietal and/or frontal bones, and slightly increased incidence of wavy, notched and incompletely ossified ribs. HD: Malformations: anasarca (generalized subcutaneous edema), anophthalmia (absent eyes), folded retina, small lens, cleft lip/palate, forelimb hyperflexion, small, short and/or bent limbs, brachydactyl (small digits), multiple fused ribs, omphalocele (intestine protruding into umbilicus), small liver lobes, and/or small lung lobes. Observations of small/short limbs/organs may be related to smaller fetuses at high dose. External and visceral variation: bilateral moderate dilatation of the lateral ventricles. Skeletal variation: small incisors, incomplete ossification and/or absence of cervical and thoracic vertebrae centrum and/or arches, wavy, notched and/or absent ribs, and incomplete ossification of pelvic bone.

LD: low dose; MD: mid dose; HD: high dose

Prenatal and Postnatal Development

Neither submitted nor required

5.5.5. **Other Toxicology Studies**

None

X X

M. Anwar Goheer, Ph.D.
Emily F. Wearne, Ph.D.
Primary Reviewers

Whitney Helms, Ph.D.
Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant seeks approval of brigatinib for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. The proposed brigatinib dosing regimen is 90 mg orally once daily (QD) for the first seven days, then 180 mg orally QD, with or without food.

The Clinical Pharmacology Section of the NDA is supported by single and repeat dose pharmacokinetics (PK) studies of brigatinib in cancer patients and the following evaluations and analyses: dose-response of brigatinib 90 mg QD for the first seven days, followed by 180 mg QD versus 90 mg QD, exposure-response (ER) relationships, population pharmacokinetics (popPK), effect of organ impairment and food on brigatinib PK, potential PK drug-drug interactions (DDI) between brigatinib and a strong CYP3A4 inhibitor, strong CYP3A4 inducer, and strong CYP2C8 inhibitor, and potential QT/QTc prolongation. The popPK analyses did not identify clinically important covariates influencing brigatinib PK.

Based on the positive dose-response (DR) relationship for efficacy, the proposed brigatinib dosing regimen is reasonable. An exploratory sensitivity analysis for survival was conducted using simulated varying daily exposure as a covariate. This analysis demonstrated a positive ER relationship for progression-free survival (PFS) and overall survival (OS), which is consistent with the observed positive DR relationship. DR relationships were observed for dose modifications (including dose reduction and interruption) and some treatment-related Grade 3-4 adverse events (increased creatinine phosphokinase, skin and subcutaneous tissue disorders, rash), and serious adverse events (pneumonitis, pneumonia). The ER relationship for safety based on predicted mean daily AUC of the second week is also consistent with the DR relationship. The overall efficacy and safety profiles support the use of the proposed dose (90 mg for 7 days, then 180 mg QD) with dose modification in the event of adverse reactions to the lowest dose of 60 mg.

Recommendations
The proposed brigatinib dosing regimen of 90 mg orally QD for the first seven days, then 180 mg QD, with the dose reduction schema in the event of adverse reactions is acceptable given the DR and ER relationships for efficacy and for safety. From a Clinical Pharmacology standpoint, the NDA is approvable provided that the Applicant and the FDA reach an agreement regarding the labeling language.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Proposed dosing regimen is supported by DR and ER relationships for overall response rate (ORR), PFS, and OS
General dosing instructions	Starting dose of 90 mg orally QD for the first seven days, then 180 mg QD, without regards to food.
Dosing in patient subgroups (intrinsic and extrinsic factors)	If concomitant use of a strong CYP3A inhibitor cannot be avoided, reduce the brigatinib daily dose by approximately 50% (i.e., 180 mg to 90 mg or 90 mg to 60 mg).
Labeling	• Avoid concomitant use of strong CYP3A inhibitors. If concomitant use of a strong CYP3A inhibitor cannot be avoided, reduce the brigatinib daily dose by approximately 50%. • Avoid concomitant use of strong CYP3A inducers. • Coadministration of ALUNBRIG with CYP3A substrates can result in decreased concentrations and efficacy of CYP3A substrates, including hormonal contraceptives. Advise females of reproductive potential to use an effective non-hormonal method of contraception during treatment with ALUNBRIG and for at least 4 months after the final dose. • No dose adjustment is necessary in patients with mild hepatic impairment. The PK and safety of ALUNBRIG in patients with moderate or severe hepatic impairment have not been studied. • No dose adjustment is necessary in patients with mild or moderate renal impairment. The PK and safety of ALUNBRIG in patients with severe renal impairment have not been studied.
Bridge between the to-be-marketed and clinical trial formulations	The registration trial (201) and supportive trial (101) utilized the 30 mg tablet. The to-be-marketed 30 and 90 mg tablet formulations are bioequivalent.

Postmarketing Requirements and Commitments

The Applicant is requested to conduct the following clinical pharmacology studies as a postmarketing requirement (PMR) or postmarketing commitment (PMC). The PMR/PMC studies will be included in the Approval letter with milestones agreed upon after negotiation with the Applicant.

PMC or PMR	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
☐ PMC ☒ PMR	Determination of an appropriate brigatinib dose for patients with moderate to severe hepatic impairment.	65% of the administered dose (41% as unchanged brigatinib) was recovered in the feces, indicating that hepatic elimination is the major elimination pathway.	(b) (4) [redacted] If severe hepatic impairment has an effect, moderate hepatic impairment will be evaluated.
☐ PMC ☒ PMR	Determination of an appropriate brigatinib dose for patients with severe renal impairment.	25% of the administered dose (86% as unchanged brigatinib) was recovered in the urine.	(b) (4) [redacted] If severe renal impairment has an effect, moderate renal impairment will be evaluated.
☐ PMC ☒ PMR	Determination of an appropriate brigatinib dose for patients with concomitant use of a moderate CYP3A4 inhibitor.	Coadministration of itraconazole (a strong CYP3A4 inhibitor) increased brigatinib AUC by 2-fold (90% CI: 1.8, 2.2) and C_{max} by 21% (90% CI: 13%, 30%) as compared with brigatinib alone.	Conduct a physiologically-based pharmacokinetic modeling study of the effect of repeat doses of a moderate CYP3A4 inhibitor on the single dose pharmacokinetics of brigatinib to assess the potential for excessive drug toxicity.
☒ PMC ☐ PMR	Determination of an appropriate brigatinib dose for patients with concomitant use of a moderate CYP3A4 inducer.	Coadministration of rifampin (a strong CYP3A4 inducer) decreased brigatinib AUC by 80% (90% CI: 79%, 82%) and C_{max} by 60% (90% CI: 56%, 63%) as compared with brigatinib alone.	Conduct a physiologically-based pharmacokinetic modeling study of the effect of repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of brigatinib to assess the magnitude of decreased

			drug exposure and to determine appropriate dosing recommendations.
☒ PMC ☐ PMR	Dose adjustment in patients with comedications of CYP3A4 substrates whose PK may be affected by brigatinib.	Brigatinib induces CYP3A via activation of the (pregnane X receptor (PXR)) in vitro and may decrease concentrations of CYP3A substrates.	Repeat doses of brigatinib in patients with and without coadministration of a sensitive CYP3A4 substrate.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

After a single dose and at steady-state, systemic exposure was dose proportional over the dose range of 30 mg to 240 mg QD. The geometric mean (%CV) steady-state $AUC_{0\text{-}tau}$ was 8165 (57%) and 20276 (56%) ng·h/mL following brigatinib 90 mg and 180 mg QD, respectively. The geometric mean (%CV) steady-state C_{max} was 552 (65%) and 1452 (60%) ng/mL following brigatinib 90 mg and 180 mg QD, respectively. The geometric mean accumulation ratio was 1.9 to 2.4 following brigatinib QD dosing.

Absorption

The median t_{max} is 2 hours following administration of brigatinib 90 or 180 mg QD. A high-fat meal did not affect brigatinib AUC and C_{max}.

Distribution

Brigatinib is 66% bound to human plasma proteins and binding is not concentration-dependent in vitro. The blood-to-plasma concentration ratio is 0.7. The geometric mean (%CV) apparent volume of distribution (V_d/F) of brigatinib at steady-state was 153 L (47%) following brigatinib 180 mg QD.

Metabolism

Brigatinib is primarily metabolized by CYP2C8 (72%) and CYP3A4 (28%) in vitro. N-demethylation and cysteine conjugation were the two major metabolic clearance pathways. Following a single 180 mg oral dose of ^{14}C-brigatinib, unchanged brigatinib (91.5%) and its primary metabolite AP26123 (3.5%) were the major circulating radioactive components. Steady-state AUC of AP26123 was <10% of brigatinib exposure in patients. AP26123 inhibited ALK with approximately ≤4-fold lower potency than brigatinib.

Excretion

Following a single 180 mg oral dose of ^{14}C-brigatinib in healthy subjects, 65% of the administered dose (41% as unchanged brigatinib) was recovered in the feces and 25% of the administered dose (86% as unchanged brigatinib) was recovered in the urine.

Dose- and Exposure-Response Relationships

Although there was a dose-efficacy relationship, the ER relationship for efficacy was relatively flat between the two dosing regimen arms based on the geometric mean of the steady-state trough concentrations. Considering the >30% dose interruption and dose reduction in both arms, an exploratory sensitivity analysis for survival was conducted using simulated varying daily exposure as a covariate. This analysis demonstrated a positive ER relationship for PFS and OS, which is consistent with the observed DR relationship. DR relationships were observed for dose modifications (including dose reduction and interruption) and some treatment-related Grade 3-4 adverse events (increased creatinine phosphokinase, skin and subcutaneous tissue disorders, rash), and serious adverse events (pneumonitis, pneumonia). The ER relationship for safety based on predicted mean daily AUC of the second week is also consistent with the DR relationship. The overall efficacy and safety profiles support the use of the proposed dose (90 mg for 7 days, then 180 mg QD) with dose modification in the event of adverse reactions to the lowest dose of 60 mg.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing regimen of brigatinib is 90 mg orally QD for the first seven days, then 180 mg QD, with or without food.

Therapeutic Individualization

Results of a DDI study showed that coadministration of itraconazole (a strong CYP3A4 inhibitor) increased brigatinib AUC by 2-fold (90% CI: 1.8, 2.2) and C_{max} by 21% (90% CI: 13%, 30%) as compared with brigatinib alone. Based on the dose-response relationship for safety showing increased incidence of adverse reactions and dose reductions/interruptions due to adverse reactions in Arm B (90 mg for 7 days, then 180 mg QD) compared to Arm A (90 mg QD) (Table 16) and exposure-response for safety (Figure 7), a 2-fold increase in exposure is clinically meaningful; therefore, strong CYP3A inhibitors should be avoided. For patients requiring concomitant use of a strong CYP3A inhibitor, the brigatinib once daily dose should be reduced by approximately 50% (i.e., 180 mg to 90 mg or 90 mg to 60 mg).

Outstanding Issues

The PK and safety of brigatinib in patients with severe renal impairment and moderate to severe hepatic impairment have not been studied; therefore PMR studies are requested to determine an appropriate brigatinib dose for patients with severe renal impairment and for patients with moderate to severe hepatic impairment. The labeling recommends no dose adjustment in patients with mild and moderate renal impairment and in patients with mild hepatic impairment.

Given that the DDI study showed a 2-fold increase in brigatinib exposure with coadministration of a strong CYP3A4 inhibitor and lack of clinical data in patients to inform the magnitude and clinical relevance of a potential increase in exposure with coadministration of moderate CYP3A4 inhibitors, the Applicant is requested to assess the effect of moderate CYP3A4 inhibitors on brigatinib PK and to determine dosing recommendations by conducting a physiologically-based pharmacokinetic (PBPK) modeling under a PMR. If results of the completed modeling study do not sufficiently inform the issue, the study results will be used as new safety information to subsequently require a dedicated DDI PK study. The labeling recommends avoidance of strong CYP3A inhibitors. If concomitant use of a strong CYP3A inhibitor cannot be avoided, the brigatinib daily dose should be reduced by approximately 50%.

Given that the DDI study showed an 80% decrease in brigatinib exposure with coadministration of a strong CYP3A4 inducer, the PK and potential decrease in efficacy of brigatinib in patients requiring concomitant use of a moderate CYP3A4 inducer should be studied by a PBPK modeling approach as a PMC to determine dosing recommendations in patients requiring concomitant use of a moderate CYP3A4 inducer. (b) (4) The labeling recommends avoidance of strong CYP3A4 inducers.

Brigatinib may induce CYP3A at clinically relevant concentrations based on the human hepatocytes and PXR activation study in vitro; therefore, a PMC clinical trial is requested to assess the effect of brigatinib on the magnitude of decreased exposure of a sensitive CYP3A4 substrate. The ability of brigatinib to induce CYP2C should be evaluated in vitro under the IND for brigatinib as activation of the nuclear receptor, Pregnane X receptor (PXR), results in co-induction of CYP3A and CYP2C.

Summary of Labeling Recommendations

Drug-Drug Interactions

Coadministration of itraconazole (a strong CYP3A4 inhibitor) increased brigatinib AUC by 2-fold (90% CI: 1.8, 2.2) and C_{max} by 21% (90% CI: 13%, 30%) as compared with brigatinib alone. Based on the dose-response relationship for safety showing increased adverse reactions and dose reductions/interruptions due to adverse reactions in Arm B (90/180 mg QD) compared to Arm A (90 mg QD) (Table 16) and exposure-response for safety (Figure 7), a 2-fold increase in

exposure is clinically meaningful; therefore, the labeling recommendation should state to avoid concomitant use of ALUNBRIG with strong CYP3A inhibitors. If concomitant use of a strong CYP3A inhibitor is unavoidable, the once daily dose of ALUNBRIG should be reduced by approximately 50% (i.e., 180 mg to 90 mg or 90 mg to 60 mg). After discontinuation of a strong CYP3A inhibitor, the ALUNBRIG dose that was taken prior to initiating the strong CYP3A inhibitor should be resumed.

Coadministration of rifampin (a strong CYP3A4 inducer) decreased brigatinib AUC by 80% (90% CI: 79%, 82%) and C_{max} by 60% (90% CI: 56%, 63%) as compared with brigatinib alone. Based on the dose-response relationship for efficacy showing increased ORR and PFS in Arm B (90/180 mg QD) compared to Arm A (90 mg QD), a 80% decrease in exposure is clinically meaningful; therefore, the labeling recommendation should state to avoid concomitant use of ALUNBRIG with strong CYP3A inducers. Although 70% of the patient population presented with brain metastases, an analysis of concomitant medications from Studies 201 and 101 showed that patients were generally able to avoid antiepileptics that are strong CYP3A4 inducers such as carbamazepine, phenytoin, and phenobarbital. Patients were able to receive other antiepileptics that do not induce CYP3A4 such as levetiracetam, lamotrigine, lacosamide, valproate sodium, zonisamide, gabapentin, and pregablin. The Applicant recommended avoidance of moderate CYP3A inducers as well as strong inducers. No patients received a moderate CYP3A4 inducer during brigatinib treatment in Study 201 and 101. Given the lack of clinical data in patients and a dedicated DDI study to inform the magnitude and clinical relevance of potential decrease in exposure with coadministration of moderate CYP3A4 inducers, it is not recommended to include the labeling statement to avoid moderate CYP3A inducers.

Brigatinib may induce CYP3A at clinically relevant concentrations based on the human hepatocytes and PXR activation study in vitro. Coadministration of ALUNBRIG with CYP3A substrates can result in decreased concentrations and loss of efficacy of CYP3A substrates, including hormonal contraceptives.

Contraception

The proposed patient population of ALK-positive NSCLC is generally younger than the average NSCLC population (median age of 54 years) and has a higher percentage of females than in the unselected population. Given that brigatinib is a teratogen and ALUNBRIG may cause decreased concentrations and efficacy of hormonal contraceptives (primarily metabolized by CYP3A4 and to a lesser extent by CYP2C9/CYP2C19), females of reproductive potential should be advised to use effective non-hormonal contraceptives during treatment with ALUNBRIG and for at least 4 months after the final dose.

Organ Impairment

Following oral administration of a single 180 mg dose of radiolabeled brigatinib to healthy subjects, 65% of the administered dose (41% as unchanged brigatinib) was recovered in the feces, indicating that hepatic elimination is the major elimination pathway. Based on a popPK analysis, brigatinib exposures were similar between 49 subjects with mild hepatic impairment (total bilirubin within ULN and AST >ULN or total bilirubin >1 and up to 1.5 × ULN and any AST) and 377 subjects with normal hepatic function (total bilirubin and AST within ULN). The PK and safety of brigatinib in patients with moderate (total bilirubin >1.5 and up to 3 × ULN and any AST) to severe (total bilirubin >3 × ULN and any AST) hepatic impairment have not been studied.

Following oral administration of a single 180 mg dose of radiolabeled brigatinib to healthy subjects, 25% of the administered dose (86% as unchanged brigatinib) was recovered in the urine, indicating that renal excretion is also an important elimination pathway. Based on a population pharmacokinetic analysis, brigatinib exposures were similar among 125 subjects with mild (CLcr 60 to <90 mL/min) renal impairment, 34 subjects with moderate renal impairment (CLcr 30 to <60 mL/min) and 270 subjects with normal renal function (≥90 mL/min), suggesting that no dose adjustment is necessary in patients with mild to moderate renal impairment. The PK and safety of brigatinib in patients with severe renal impairment (CLcr <30 mL/min) have not been studied.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Brigatinib (molecular weight of 584 g/mol) exhibits linear PK in the dose range of 30 to 240 mg. Single and repeat dose brigatinib exposures at the approved recommended dosages are shown in Table 14. A summary of general pharmacology and PK characteristics of brigatinib is shown in Table 15.

Table 14: Brigatinib Exposures at Approved Recommended Dosages

	Dosage, once daily	
	90 mg	**180 mg**
Single Dose		
Geometric Mean AUC_{0-24h}, ng·h/mL (%CV)	4900 (61%) n=50	11834 (51%) n=44
Geometric Mean C_{max}, ng/mL (%CV)	418 (64%) n=50	1037 (57%) n=44
Repeat Doses		
Geometric Mean AUC_{0-Tau}, ng·h/mL (%CV)	8165 (57%) n=15	20276 (56%) n=63
Geometric Mean C_{max}, ng/mL (%CV)	552 (65%) n=15	1452 (60%) n=63
Geometric C_{min}, ng/mL (%CV)	226 (57%) n=15	520 (61%) n=63

Table 15: Summary of General Pharmacology and Pharmacokinetic Characteristics of Brigatinib

Pharmacology	
Mechanism of Action	• Inhibited EML4-ALK with an IC_{50} of 14 nM and IC_{90} of 38 nM. • Inhibited 17 ALK secondary mutations associated with resistance to crizotinib (IC_{50} ranging from 9-184 nM and IC_{90} ranging from 22-762 nM).
Active Moieties	Unchanged brigatinib (91.5%) and its primary metabolite AP26123 (3.5%, <10% of AUC of brigatinib) were the major circulating components at steady-state. AP26123 inhibited ALK with approximately ≤4-fold lower potency than brigatinib in kinase and cellular assays in vitro.
QT Prolongation	Brigatinib inhibited hERG with IC_{50} >10 µM in vitro. The QT interval prolongation potential of brigatinib was assessed in 123 patients with advanced solid tumors following brigatinib 30 mg to 240 mg QD. The maximum mean QTcF (corrected QT by the Fridericia method) change from baseline was <10 ms. An exposure-QT analysis suggested no concentration-dependent QTc interval prolongation.
General Information	
Bioanalysis	Brigatinib was measured using validated LC-MS/MS assay methods over the single concentration range of 25 to 2500 ng/mL [Method BAC-AI-L004] and dual ranges of 0.1 to 7.5 ng/mL (low range) and 5 to 500 ng/mL (high range) [Method BAC-AI-L003]. The metabolite AP26123 was measured using validated LC-MS/MS assay methods over the single concentration range of 2 to 200 ng/mL [Method BAC-AI-L004] and dual ranges of 0.02 to 1.5 ng/mL (low range) and 1 to 100 ng/mL (high range) [Method BAC-AI-L003]. Accuracy (%RE) and precision (%CV) of the quality controls (QCs) for the runs used in measuring brigatinib and AP26123 concentrations were ≤15%, which are acceptable based on the current Bioanalytical Method Validation Draft FDA Guidance for Industry.
Healthy vs. Patients	PK characteristics were similar between healthy subjects and the target patient population.

Drug Exposure at Steady State Following the Therapeutic Dosing Regimen	• Following brigatinib 90 mg QD in patients, geometric mean (%CV) AUC_{0-tau} was 8165 ng·h/mL (57%) and C_{max} was 552 ng/mL (65%). • Following brigatinib 180 mg QD in patients, geometric mean (%CV) AUC_{0-tau} was 20276 ng·h/mL (56%) and C_{max} was 1452 ng/mL (60%).
Range of Effective Dose or Exposure	The minimally effective brigatinib dose resulting in mean steady-state trough concentrations that exceed the IC_{50} for inhibition of EML4-ALK and 17 ALK secondary mutations associated with clinical resistance to crizotinib is 60 mg. Following 60 mg QD, the steady-state maximum concentrations exceed the IC_{90} for inhibition of EML4-ALK and 17 ALK secondary mutations associated with clinical resistance to crizotinib.
Maximally Tolerated Dose or Exposure	The maximum tolerated dose (MTD) was not reached at the highest evaluated dose of 300 mg QD.
Dose Proportionality	After a single dose and at steady-state, brigatinib systemic exposure was dose proportional over the range of 30 mg to 240 mg QD. After a single dose of 30 to 300 mg, exposures were approximately dose proportional with an estimated slope of 1.2 (90% CI: 1.0, 1.4) for AUC_{0-24h} and 1.2 (90% CI: 0.96, 1.3) for C_{max} using a power model. After repeat doses of 30 to 240 mg, exposures were approximately dose proportional with an estimated slope of 1.2 (90% CI: 1.0, 1.4) for AUC_{ss} and 1.2 (90% CI: 0.96, 1.4) for $C_{max,ss}$.
Accumulation	The geometric mean accumulation ratio following brigatinib 180 mg QD was 1.9 to 2.4-fold.
Variability	• Following brigatinib 90 mg QD, the inter-subject variability (CV%) of steady-state AUC_{0-tau} was 57% and C_{max} was 65%. • Following brigatinib 180 mg QD, the CV% of steady-state AUC_{0-tau} was 56% and C_{max} was 60%.
Absorption	
Bioavailability	The 30 mg and 90 mg tablet formulations for oral administration were bioequivalent (geometric mean ratios and 90% CI for AUC and C_{max} fell within the boundaries of 80% to 125%).
T_{max}	• Following brigatinib 90 mg QD, the median t_{max} is 2 hours (range 1 to 8 hours). • Following brigatinib 180 mg QD, the median t_{max} is 2.1 hours (range 0.5 to 6.2 hours).
Food effect [a] (Fed/fasted)	**$AUC_{0-\infty}$** / **C_{max}** / **T_{max}** Geometric Mean Ratio [90% CI] 0.98 [0.894-1.07] / Geometric Mean Ratio [90% CI] 0.87 [0.783-0.968] / Increased by a median of 3 hours [a] After a high-fat meal consisting of approximately 920 calories and 57.8 grams carbohydrate (25%, ~230 calories), 58.9 grams fat (58%, ~530 calories), and 39.5 grams protein (17%, ~160 calories).
Distribution	
Volume of Distribution	Following brigatinib 180 mg QD, the geometric mean (%CV) apparent volume of distribution (V_d/F) at steady-state was 153 L (47%).
Plasma Protein Binding	Brigatinib is 66% bound to human plasma proteins and the binding is not concentration-dependent in vitro.
As Substrate of Transporters	• Substrate of p-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). • Not a substrate of organic anion transporting polypeptide (OATP1B1,

	OATP1B3), organic anion transporter (OAT1, OAT3), organic cation transporter (OCT1, OCT2), multidrug and toxin extrusion protein (MATE1, MATE2K), or bile salt export pump (BSEP).
Elimination	
Terminal Elimination Half-Life	The mean (%CV) elimination half-life ($t_{1/2}$) of brigatinib at steady-state was 25 hours (30%). Following oral administration of brigatinib 180 mg once daily, the mean (%CV) apparent oral clearance (CL/F) of brigatinib at steady-state is 12.7 L/h (70%).
Effective Elimination Half-Life	The effective $t_{1/2}$ is similar to the terminal elimination $t_{1/2}$.
Metabolism	
Fraction Metabolized (% dose)	Based on the mean percentage of the dose recovered as metabolites in the excreta, the fraction metabolized is 42%.
Primary Metabolic Pathway(s)	The major metabolic pathways of brigatinib is N-demethylation and cysteine conjugation to form AP26123 by CYP2C8 (72%) and CYP3A4 (28%) in vitro.
Excretion	
Primary Excretion Pathways (% dose) ±SD	• Feces: 65% ± 2.4% (41% unchanged brigatinib). • Urine: 25% ± 1.9% (86% unchanged brigatinib).
Interaction liability (Drug as Perpetrator)	
Inhibition/Induction of Metabolism	• Not an inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5 in vitro. • Brigatinib activated pregnane X receptor (PXR) in vitro, which may co-induce CYP3A and CYP2C; Induction of CYP3A4 mRNA (mean 6-fold change at 1 μM), but no induction of CYP3A4 activity. • Not an inducer of CYP1A2 or CYP2B6 mRNA or activity. • Coadministration of itraconazole (a strong CYP3A4 inhibitor) 200 mg BID with a single dose of 90 mg brigatinib increased brigatinib AUC by 2-fold (90% CI: 1.8, 2.2) and C_{max} by 21% (90% CI: 13%, 30%) as compared with brigatinib alone. • Coadministration of rifampin (a strong CYP3A4 inducer) 600 mg QD with a single dose of 180 mg brigatinib decreased brigatinib AUC by 80% (90% CI: 79%, 82%) and C_{max} by 60% (90% CI: 56%, 63%) as compared with brigatinib alone. • Coadministration of gemfibrozil (a strong CYP2C8 inhibitor) 600 mg BID with a single dose of 90 mg brigatinib decreased brigatinib AUC by 12% (90% CI: 6%, 17%) and C_{max} by 41% (90% CI: 35%, 46%) as compared with brigatinib alone.
Inhibition/Induction of Transporter Systems	• Inhibitor of P-gp, BCRP, OCT1, MATE1 and MATE2K in vitro. • Not an inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, or BSEP in vitro.

* PK parameters are presented as geometric mean (%CV) or median (minimum, maximum) unless otherwise noted.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Two dosing regimens were evaluated in Study AP26113-13-201 to provide evidence of effectiveness: 90 mg QD (Arm A) and 90 mg QD for the first 7 days, then 180 mg QD (Arm B). Exploratory dose-response analyses suggested the following:

- Arm B (90/180 mg) delivered a higher ORR (54% [95% CI: 44%, 63%] in Arm B versus 45% [95% CI: 35%, 54%] in Arm A).
- Arm B resulted in a higher intracranial ORR (67% [95% CI: 41%, 87%] in Arm B versus 42% [95% CI: 23%, 63%] in Arm A) in patients with brain metastases at baseline.
- Arm B showed an increase in median progression-free survival (15.6 months in Arm B versus 9.2 months in Arm A) according to the Applicant's analysis.
- Patients in Arm B had a higher rate of 1-year overall survival (79.5% versus 70.6%) according to the Applicant's analysis.
- Patients in Arm B had fewer discontinuations and fewer deaths due to disease progression.
- Duration of response was higher in Arm A than in Arm B (13.8 versus 11.1 months).

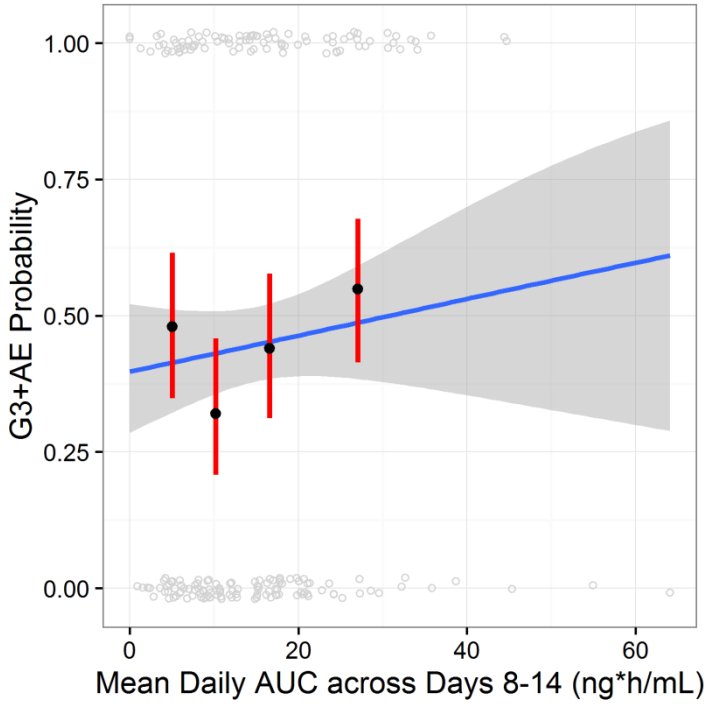
Although there was a dose-efficacy relationship, the ER relationship for efficacy was relatively flat between the two arms based on the geometric mean of the steady-state trough concentrations. Considering the >30% dose interruption and dose reduction in both arms, an exploratory sensitivity analysis for survival was conducted using simulated varying daily exposure as a covariate. This analysis demonstrated a positive ER relationship for PFS and OS, which is consistent with the observed DR relationship. DR relationships were observed for dose modifications (including dose reduction and interruption) and some treatment-related Grade 3-4 adverse events (increased creatinine phosphokinase, skin and subcutaneous tissue disorders, rash), and serious adverse events (pneumonitis, pneumonia). The ER relationship for safety based on predicted mean daily AUC of the second week is also consistent with the DR relationship. The overall efficacy and safety profiles support the use of the proposed dose (90 mg for 7 days, then 180 mg QD) with dose modification in the event of adverse reactions to the lowest dose of 60 mg.

Table 16: Summary of Safety Endpoints in Study 201 that Showed Dose-Response Relationship

	Arm A, 90 mg QD N=109	**Arm B, 90 mg QD → 180 mg QD, N=110**
Drug Exposure		
Dose Interruption of ≥3 days, n (%)	20 (18.3)	40 (36.4)
Dose Interruption due to AE, n (%)	35 (32.1)	50 (45.5)
Duration of Longest Dose Interruption ≥3 days, Mean±SD (n), Min, Median, Max	8.8±3.43 (20), 4, 7.5, 16	12.9±10.15 (40), 3, 9.5, 57
Any Treatment Emergent AE		
Any treatment-related SAE, n (%)	8 (7.3)	18 (16.4)
Any treatment-related TEAE Grade ≥3	21 (19.3)	34 (30.9)

	Arm A, 90 mg QD N=109	Arm B, 90 mg QD → 180 mg QD, N=110
Any treatment-related SAE Grade ≥3, n (%)	6 (5.5)	10 (9.1)
Any TEAE leading to dose interruption, dose reduction, or brigatinib discontinuation, n (%)	36 (33.0)	55 (50.0)
Any TEAE leading to brigatinib discontinuation (primary reason), n (%)	3 (2.8)	9 (8.2)
Patients with ≥1 Treatment Related AE		
Diarrhea, n (%)	15 (13.8)	31 (28.2)
Blood creatinine phosphokinase increased, n (%)	9 (8.3)	31 (28.2)
Amylase increased, n (%)	8 (7.3)	15 (13.6)
Treatment-Related Grade ≥3 AE		
Blood Creatinine Phosphokinase Increased	2 (1.8)	8 (7.3)
Skin And Subcutaneous Tissue Disorders	2 (1.8)	5 (4.5)
Rash	1 (0.9)	3 (2.7)
Treatment-Emergent SAE		
Pneumonitis	2 (1.8)	8 (7.3)
Pneumonia	3 (2.8)	8 (7.3)
Source: Study 201 Final Study Report, Tables 12-1, 12-2, 12-3, 12-4, and 12-9.		

Figure 7: Plot of Probability of Experiencing a ≥ Grade 3 AE by Mean Daily Exposure of the Second Week



Source: FDA reviewer's analysis.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dosing regimen of 90 mg orally QD for the first seven days, then 180 mg QD, is appropriate for the general patient population for which the indication is being sought. The proposed dose reduction strategy in the event of adverse reactions to the lowest acceptable dose of 60 mg QD is reasonable as the minimally effective brigatinib dose resulting in mean steady-state trough concentrations that exceed the IC_{50} for inhibition of EML4-ALK and 17 ALK secondary mutations associated with clinical resistance to crizotinib is 60 mg. Following 60 mg QD, the steady-state maximum concentrations exceed the IC_{90} for inhibition of EML4-ALK and 17 ALK secondary mutations associated with clinical resistance to crizotinib.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

A comparative population PK analysis showed that brigatinib exposures were similar between 49 subjects with mild hepatic impairment (total bilirubin within upper limit of normal [ULN] and AST greater than ULN or total bilirubin greater than 1 and up to 1.5 times ULN and any AST) and 377 subjects with normal hepatic function (total bilirubin and AST within ULN). Brigatinib exposures were similar among 125 subjects with mild (CLcr 60 to less than 90 mL/min) renal impairment, 34 subjects with moderate renal impairment (CLcr 30 to less than 60 mL/min), and 270 subjects with normal renal function (greater than or equal to 90 mL/min). No dose adjustment is necessary in patients with mild hepatic impairment and in patients with mild and moderate renal impairment. Studies to determine an appropriate brigatinib dose for patients with moderate to severe hepatic impairment and for patients with severe renal impairment are requested as PMRs.

Based on a population PK analysis, age (range 18 to 83 years), race (69% Whites, 23% Asian, 6% Blacks, 2% Others), sex (48% male), body weight (range 41 to 172 kg), and albumin concentration (20-56 g/L) have no clinically meaningful effects on the PK of brigatinib; therefore, dose adjustments based on these intrinsic factors are not necessary.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Food-Drug Interactions

The effect of food on brigatinib PK was evaluated in a single 180 mg dose, randomized, two period crossover study with a 16-day washout period in 21 healthy subjects who received the 90 mg to-be-marketed tablet formulation (Study AP26113-16-109). The total calories and composition of the high-fat meal (approximately 920 calories, 58 grams carbohydrate, 59 grams fat and 40 grams protein) were consistent with the recommendations in the Food Effect FDA Guidance for Industry. PK samples were adequately collected from pre-dose to 168 hours post-dose. Administration of a single 180 mg dose of brigatinib with a high-fat, high-calorie meal in

healthy subjects resulted in no change in AUC and 13% decrease in C_{max} and increased t_{max} by a median of 3 hours as compared to fasted conditions (Table 17). A preliminary food effect study in 8 healthy subjects administered the 30 mg tablet formulation (AP26113-13-103) showed similar results; a high-fat meal resulted in no change in AUC and 24% decrease in C_{max}. These results support the labeling recommendation of administering brigatinib with or without food.

Table 17: PK Parameters of a Single Dose of Brigatinib after a High-Fat Meal as Compared with a Fasted State

Exposure Parameter	Geometric Mean (%CV)		
	High-Fat Meal	Fasted State	Geometric Mean Ratio* (90% CI)
$AUC_{0\text{-}168h}$ (ng·hr/mL)	12742 (26.7) n=24	13054 (30.1) n=21	0.98 (0.894-1.07)
$AUC_{0\text{-}inf}$ (ng·hr/mL)	12944 (26.6) n=24	13261 (29.8) n=21	0.98 (0.894-1.07)
C_{max} (ng/mL)	605 (25.2) n=24	701 (36.6) n=21	0.87 (0.783-0.968)

* Brigatinib 90 mg (to-be-marketed tablet) administered with a high-fat meal (test) vs. a fasted state (reference)

Source: AP26113-16-109 Final Study Report; Tables 7, 8; Pages 49, 50.

Drug-Drug Interactions

Effects of Other Drugs on Brigatinib

The effects of itraconazole (a strong CYP3A4 inhibitor), rifampin (a strong CYP3A4 inducer), and gemfibrozil (a strong CYP2C8 inhibitor) on brigatinib PK were evaluated in a single dose, randomized, crossover study with a washout period of 16 days in healthy subjects (Study AP26113-15-105). PK samples for brigatinib were adequately collected from pre-dose to 120 hours post-dose.

Strong CYP3A Inhibitors: Coadministration of itraconazole 200 mg BID for 5 days with a single dose of 90 mg brigatinib increased brigatinib AUC by 2-fold (90% CI: 1.8, 2.2) and C_{max} by 21% (90% CI: 13%, 30%) as compared with brigatinib alone (Table 18). Clearance (CL/F) of brigatinib was decreased by 52% from 14 L/h to 6.7 L/h with coadministration of itraconazole. Based on the dose-response relationship for safety showing increased incidence of adverse reactions and dose reductions/interruptions due to adverse reactions in Arm B (90/180 mg QD) compared to

Arm A (90 mg QD) (Table 16) and exposure-response for safety (Figure 7), a 2-fold increase in exposure is clinically meaningful; therefore, concomitant use of strong CYP3A inhibitors with brigatinib should be avoided. For patients requiring concomitant use of a strong CYP3A inhibitor, the brigatinib once daily dose should be reduced by approximately 50% (i.e., 180 mg to 90 mg or 90 mg to 60 mg). Given the lack of clinical data in patients to inform the magnitude and clinical relevance of a potential increase in exposure with coadministration of moderate CYP3A4 inhibitors, the Applicant is requested to assess the effect of moderate CYP3A4 inhibitors on brigatinib PK and to determine dosing recommendations by conducting either a PBPK modeling or dedicated DDI study under a PMR.

Table 18: Comparative Analysis of Brigatinib PK Parameters on Day 1 (Without Itraconazole) and Day 21 (With Itraconazole)

	Geometric Mean (%CV)		
Exposure parameter	**Brigatinib alone (90 mg)**	**Brigatinib (90 mg) with itraconazole (200 mg BID for 7 days)**	**Geometric Mean Ratio* (90% CI)**
$AUC_{0\text{-}120h}$ (ng·hr/mL)	6139 (28.5) n=20	11178 (31.2) n=20	1.82 (1.72, 1.93)
$AUC_{0\text{-}inf}$ (ng·hr/mL)	6452 (28.7) n=20	13501 (35.6) n=11	2.01 (1.84, 2.20)
C_{max} (ng/mL)	331 (31.9) n=20	401 (38.4) n=20	1.21 (1.13, 1.30)

* Brigatinib 90 mg alone vs. brigatinib 90 mg and itraconazole 200 mg BID for 5 days

Source: AP26113-15-105 Final Study Report, Tables 14, 16, Pages 96, 100.

Strong CYP3A Inducers: Coadministration of rifampin 600 mg QD for 7 days with a single dose of 180 mg brigatinib decreased brigatinib AUC by 80% (90% CI: 79%, 82%) and C_{max} by 60% (90% CI: 56%, 63%) as compared with brigatinib alone (Table 19). Clearance (CL/F) of brigatinib was increased by 4.1-fold from 11.5 L/h to 59 L/h with coadministration of rifampin; therefore, concomitant use of strong CYP3A inducers with brigatinib should be avoided. Although 70% of the patient population presented with brain metastases, an analysis of concomitant medications from Study 201 and Study 101 showed that patients were generally able to avoid antiepileptics that are strong CYP3A4 inducers such as carbamazepine, phenytoin, and phenobarbital. Patients were able to receive other antiepileptics that do not induce CYP3A4 such as levetiracetam, lamotrigine, lacosamide, valproate sodium, zonisamide, gabapentin, and pregablin. No patients received a moderate CYP3A4 inducer during brigatinib treatment in

Study 201 and Study 101. Given the lack of clinical data in patients to inform the magnitude and clinical relevance of a potential decrease in exposure with coadministration of moderate CYP3A4 inducers, the applicant is requested to assess the effect of moderate CYP3A4 inducers on brigatinib PK and to determine dosing recommendations by conducting either a PBPK modeling or dedicated DDI study under a PMC.

Table 19. Comparative Analysis of Brigatinib PK Parameters on Day 1 (Without Rifampin) and Day 23 (With Rifampin)

	Geometric Mean (%CV)		
Exposure parameter	**Brigatinib alone (180 mg)**	**Brigatinib (180 mg) with rifampin (600 mg QD for 7 days)**	**Geometric Mean Ratio* (90% CI)**
$AUC_{0\text{-}120h}$ (ng·hr/mL)	15143 (33.8) n=20	3019 (25.7) n=19	0.20 (0.19, 0.22)
$AUC_{0\text{-}inf}$ (ng·hr/mL)	15616 (34.4) n=20	3042 (25.8) n=19	0.20 (0.18, 0.21)
C_{max} (ng/mL)	826 (31.2) n=20	334 (29.2) n=19	0.40 (0.37, 0.44)

* Brigatinib 180 mg alone vs. brigatinib 180 mg and rifampin 600 mg QD for 7 days

Source: AP26113-15-105 Final Study Report, Tables 10, 12, Pages 80, 84.

Strong CYP2C8 Inhibitors: Coadministration of gemfibrozil 600 mg BID for 5 days with a single dose of 90 mg brigatinib decreased brigatinib AUC by 12% (90% CI: 6%, 17%) and C_{max} by 41% (90% CI: 35%, 46%) as compared with brigatinib alone (Table 20). Clearance (CL/F) of brigatinib was increased by 20% from 13.1 L/h to 15.7 L/h with coadministration of gemfibrozil. The unexpected decrease in AUC and expected increase in clearance with gemfibrozil coadministration are not clinically meaningful.

Table 20. Comparative Analysis of Brigatinib PK Parameters on Day 1 (Without Gemfibrozil) and Day 21 (With Gemfibrozil)

	Geometric Mean (%CV)		
Exposure parameter	**Brigatinib alone (90 mg)**	**Brigatinib (90 mg) with gemfibrozil (600 mg BID for 5 days)**	**Geometric Mean Ratio* (90% CI)**
$AUC_{0\text{-}120h}$ (ng·hr/mL)	6488 (34.2) n=20	5340 (27.5) n=19	0.85 (0.80, 0.91)
$AUC_{0\text{-}inf}$ (ng·hr/mL)	6875 (33.9) n=19	5742 (25.7) n=19	0.88 (0.83, 0.94)
C_{max} (ng/mL)	348 (40.5) n=20	199 (35.8) n=19	0.59 (0.54, 0.65)

* Brigatinib 90 mg alone vs. brigatinib 90 mg and gemfibrozil 600 mg BID for 5 days

Source: AP26113-15-105 Final Study Report, Tables 6, 8, Pages 64, 68.

P-gp and BCRP Inhibitors: In vitro studies indicated that brigatinib is a substrate of the efflux transporters, P-gp and BCRP. Given that brigatinib exhibits high solubility and high permeability in vitro, P-gp and BCRP inhibitors are unlikely to increase plasma concentrations of brigatinib. According to the 2012 draft FDA DDI Guidance, intestinal absorption is not a rate-limiting step for drugs that are highly permeable and highly soluble such as brigatinib; therefore, it is acceptable to not conduct in vivo evaluation of brigatinib with a P-gp or BCRP inhibitor.

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

Effects of Brigatinib on Other Drugs

CYP Substrates: Brigatinib and its primary metabolite, AP26123, did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5 at clinically relevant concentrations (R_1 values ≤ 1.1, Table 21).

Table 21: IC_{50} and Calculated R_1 values for Brigatinib Inhibition of CYP activities in Human Liver Microsomes

CYP Enzyme	Substrate	Brigatinib IC_{50} (μM)	AP26123 IC_{50} μM	R_1 value $(1+I/K_i)$
CYP1A2	Phenacetin	> 100	> 100	1.0
CYP2B6	Bupropion	> 100	> 100	1.0
CYP2C8	Amodiaquine	> 100	> 100	1.0
CYP2C9	Diclofenac	> 100	> 100	1.0
CYP2C19	S-Mephenytoin	> 100	> 100	1.0
CYP2D6	Dextromethorphan	> 100	> 100	1.0
CYP3A4/5	Midazolam	72.9	63.8	1.1
CYP3A4/5	Testosterone	> 100	> 100	1.0

Calculation of brigatinib R_1 values based on maximal steady-state concentration of 1452 ng/mL or 2.5 μM and 111 ng/mL or 0.2 μM [I]
K_i assumed to be $IC_{50}/2$ for competitive inhibition for those CYP enzymes without an experimental K_i value

Source: ARP212 Final Study Report, Table 6, Page 16.

Brigatinib may induce CYP3A at clinically relevant concentrations (2.5 μM) based on the human hepatocytes and PXR activation study in vitro (Table 22); therefore, a PMC clinical trial is requested to assess the magnitude of decreased exposure of a sensitive CYP3A4 substrate due to brigatinib. Given that brigatinib activates PXR, which results in co-induction of CYP3A and CYP2C, the ability of brigatinib to induce CYP2C should be evaluated in vitro under the IND for brigatinib.

Table 22: Brigatinib Induction of Mean mRNA and Activity Levels of CYP Enzymes

	CYP1A2		CYP2B6		CYP3A4	
Brigatinib (μM)	mRNA	Activity	mRNA	Activity	mRNA	Activity
0.25	1.2	0.85	1.4	1.0	3.2	1.2
1.0	0.80	0.75	2.6	1.1	5.7	1.4
2.5	0.43	0.62	2.4	0.98	4.5	1.0
5.0	0.22	0.48	1.9	0.82	2.6	0.64
7.5	0.18	0.47	1.4	0.69	1.5	0.45
10	0.13	0.44	1.3	0.59	1.1	0.35
20	0.34	0.36	0.78	0.36	0.33	0.20
Known positive inducer[a]	102	24.3	7.3	7.6	19.2	5.8

[a] Omeprazole 50 μM for CYP1A2, phenobarbital 750 μM for CYP2B6, rifampin 20 μM for CYP3A4
[b] Mean fold change relative to vehicle control from three human hepatocyte lots

Source: (b)(4)123144 Final Study Report, Figures 10, 12, 14, 16, 18, 20, Pages 50, 53, 56, 59, 62, 65.

Due to potential of brigatinib to induce CYP3A at clinically relevant concentrations, coadministration of brigatinib with CYP3A substrates can result in decreased concentrations and loss of efficacy of CYP3A substrates, including hormonal contraceptives. Estrogen and progestin hormonal contraceptives (including ethinyl estradiol, drospirenone, norgestimate, levonorgestrel, desogestrel, norethindrone, gestodene, norgestrel, ethynodiol diacetate, estradiol valerate, dienogest, ulipristal, etonogestrel, medroxyprogesterone acetate, norelgestromin), administered orally or by other non-oral routes (e.g., vaginal ring, intramuscular injection, transdermal patch, subdermal implant, hormone-releasing intrauterine devices), are primarily metabolized by CYP3A4 and to a lesser extent by CYP2C9/CYP2C19.

The proposed patient population of ALK-positive NSCLC is generally younger than the average NSCLC population (median age of 54 years) and has a higher percentage of females than in the unselected population. Given that brigatinib is a teratogen and may cause decreased concentrations and efficacy of hormonal contraceptives, females of reproductive potential should be advised to use effective non-hormonal contraception during treatment with brigatinib and for at least 4 months after the final dose of brigatinib.

Transporter Substrates: Brigatinib is an inhibitor of P-gp, BCRP, OCT1, and MATE1, MATE2K in vitro ($C_{max}/IC_{50} \geq 0.1$, Table 23); therefore, brigatinib may have the potential to increase concentrations of coadministered substrates of these transporters.

Table 23: IC_{50} and Calculated R values for Brigatinib Inhibition of Transporters

Transporter	Substrate	Brigatinib IC_{50} (µM)	C_{max} [a]/IC_{50}
P-gp	Digoxin	1.76	1.42
BCRP	Cladribine	10.1	0.25
OCT1	MPP+	N/A [b]	N/A
MATE1	Metformin	0.832	3.00
MATE2K	ASP	N/A [c]	N/A

[a] Plasma maximal steady-state concentration (C_{max}) of 1452 ng/mL or 2.5 µM
[b] IC_{50} not calculated; 89% inhibition at 65 µM
[c] IC_{50} not calculated; 60% inhibition at 20 µM

Source: 13ARIAP1R2 Final Study Report, Tables 47, 53, 67, Pages 45, 49, 60.

X	X
Ruby Leong, Ph.D. Primary Reviewer	Hong Zhao, Ph.D. Team Leader
X	X
Hongshan Li, Ph.D. Primary Reviewer	Jiang Liu, Ph.D. Team Leader

7 Statistical and Clinical and Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

Table 24 below lists the clinical trials included in the NDA submission. The primary evidence to support the clinical efficacy of brigatinib in patients with metastatic ALK-positive NSCLC who progressed on or were intolerant to crizotinib is from AP26113-13-201 (hereafter referred to as Trial ALTA).

The primary safety data used to characterize the safety profile of brigatinib in patients with metastatic ALK-positive NSCLC are also from Trial ALTA. One additional trial also provided supportive safety data, AP26113-11-101, a single-arm dose-finding and cohort expansion study of various doses of brigatinib in 137 patients. The integrated summary of safety includes patients from both trials who received any dose of brigatinib, unless otherwise specified.

Table 24: Listing of Clinical Trials Relevant to Clinical Review of NDA (Reviewer Table)

Trial Identity	Trial Design	Regimen/ schedule/ route	Endpoint(s)	Median Treatment Duration/ Follow Up	No. of patients enrolled	No. of Centers and Countries
Pivotal Study to Support Efficacy and Safety						
AP26113-13-201 (ALTA)	Randomized, non-comparative, open-label multicenter study in adult patients with advanced ALK-positive NSCLC with progression on crizotinib	Arm A: 90 mg once daily orally for 28 days per cycle (N=112) Arm B: 90 mg once daily for 7 days, then 180 mg once daily orally for 28 days per cycle (N=110)	Primary: ORR by investigator Secondary: ORR by IRC, CNS response, time to response, DoR, time on treatment, DCR, PFS, OS, safety and tolerability, PK, PROs	7.8 months	222	71 sites in 18 countries
Supportive Study for Safety						
AP26113-11-101	Single arm open-label, dose-finding and cohort expansion study in adult patients with advanced malignancies (excluding leukemia) refractory to standard therapy	Dose-finding: various Cohort expansion by disease type Total daily dose of: • 90 mg (N=18) • 120 mg (N=18) • 180 mg (N= 48) • 240-300 mg (N=15)	Phase I: RP2D Phase II: ORR CNS response (cohort 5 only)	28.3 months	137*	9 sites in 2 countries

* 71 of 79 ALK-positive NSCLC patients were previously treated with crizotinib.

ORR – objective response rate, IRC-independent review committee, RP2D - recommended phase II dose, CNS - central nervous system, DoR – duration of response, DCR – disease control rate, PFS – progression free survival, OS – overall survival, PK – pharmacokinetics, PRO – patient reported outcomes

7.1.2. Review Strategy

The FDA statistical and clinical NDA review consisted of one primary clinical reviewer, Dr. M. Naomi Horiba, and one primary statistical reviewer, Dr. Thomas Ly.

The NDA submission contained one randomized non-comparative trial, Trial ALTA, entitled "A Randomized Phase 2 Study of AP26113 in Patients with ALK-positive, Non-small Cell Lung Cancer (NSCLC) Previously Treated with Crizotinib" to support the indication. The NDA contained a second trial, AP26113-11-101 entitled "A Phase 1/2 Study of the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-Tumor Activity of the Oral ALK/EGFR Inhibitor AP26113" to support the safety analysis. The review of efficacy is based on Trial ALTA including the Clinical Study Report (CSR), case-report forms (CRFs), statistical analysis plan (SAP), datasets, and SAS program.

The clinical review of safety primarily evaluated the safety population of Trial ALTA, defined as patients who received at least one dose of study drug and consisted of 219 patients (209 received brigatinib at 90 mg daily and 210 received brigatinib at 90 mg daily for 7 days followed by 180 mg daily). The review of safety also included an evaluation of AP26113-11-101 entitled "A Phase 1/2 Study of the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-Tumor Activity of the Oral ALK/EGFR Inhibitor AP26113." The review of safety considered the CSR, SAS datasets, CRFs, and case narratives.

Data Sources

The electronic submission received on August 29, 2016, is located in the following network path: \\CDSESUB1\evsprod\NDA208772\208772.enx (SDN 5). The submission included protocols, the statistical analysis plan (SAP), CSRs, Statistical Analysis System (SAS) transport datasets in in legacy, SDTM, and ADAM format, and SAS codes for the NDA submission.

Using the primary data from Trial ALTA and AP26113-11-101, the clinical reviewer confirmed the Applicant's safety analyses by conducting analyses of primary data using MedDRA Adverse Event Diagnosis Service (MAED) and JMP programs. Methods used to perform analyses for specific issues (i.e., detailed assessment of a particular safety issue), are explained in the pertinent section of the review.

Data and Analysis Quality

The statistical reviewer was able to replicate the Applicant's primary analysis and other submitted efficacy results based on the submitted data. The report and analysis plan was provided in the NDA submission. Upon further clarification from the Applicant per FDA information requests (IRs), the reviewer was able to:

- Reproduce the applicant's analysis datasets from the raw datasets
- Evaluate documentation of data quality control/assurance procedures

7.2. Review of Relevant Individual Trials Used to Support Efficacy

7.2.1. ALTA (AP26113-13-201)

Trial Design and Endpoints

ALTA is a randomized, non-comparative, open-label, multicenter trial designed to evaluate the anti-tumor activity of brigatinib at two doses in patients with metastatic ALK-positive NSCLC who have previously received crizotinib.

Patients were randomized (1:1) to one of two doses of brigatinib:

- Arm A - 90 mg orally daily for 28 days per cycle
- Arm B - 90 mg orally daily for 7 days, then 180 mg orally daily for 28 days per cycle

Treatment continued until disease progression or unacceptable treatment-related toxicity. Patients on Arm A being treated at 90 mg QD who experienced progressive disease were allowed to escalate their dose to 180 mg QD at the discretion of the treating investigator. Patients in either arm who experienced disease progression could continue treatment at the same dose if in the opinion of the treating investigator they continued to experience benefit. Disease assessments were conducted every 4 weeks during Cycles 3-15 and every 12 weeks thereafter.

Randomization was stratified by brain metastases (present vs absent) and response to prior crizotinib (complete response [CR] or partial response [PR] vs other or unknown). The primary objective was confirmed objective response rate (ORR) by investigator assessment. Secondary objectives were as follows:

- Assess disease control rate (DCR), time to/duration of response, progression-free survival (PFS), overall survival (OS), and time on treatment.
- Assess CNS response and PFS in patients who have active brain metastases
- Assess safety and tolerability of brigatinib in study patients
- 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).

Statistical Analysis Plan

ORR

The primary endpoint was objective response rate, assessed by the investigator, defined as the proportion of the patients who were confirmed to have achieved CR or PR, per RECIST v1.1.

Confirmed responses were those that persisted on repeat imaging 4 weeks (allowing a minus 3-day time window) or more after initial response. To determine ORR, best response (CR, PR, stable disease [SD], or progressive disease [PD]) was derived for each patient who received at least one dose of study treatment. Patients with no measurable disease at baseline or no adequate post-baseline radiographic response assessment were included as non-responders in the primary efficacy endpoint analysis. The best response in target lesions (including pathological lymph nodes) per RECIST v1.1 were calculated as the maximum unsigned decrease (or the minimum increase if no decrease) in percentage in the sum of the longest dimensions of the target lesions at a single assessment compared to baseline.

Additional details of the ORR evaluation were as follows:

- Baseline disease evaluations were performed as close as possible to the study treatment start and never more than 21 days before the beginning of the study treatment.
- The best overall response was the best response recorded across all time points from initiation of study treatment until the end-of-treatment disease assessment taking into account any requirement for confirmation (i.e., in the determination of best confirmed overall response versus best overall response).
- Duration of response (DoR) was calculated as the time from the date of first response until disease progression. Duration of response was summarized with Kaplan-Meier-based descriptive statistics for patients with confirmed CR or PR that include the median DoR and corresponding 95% CIs. Subjects without disease progression were censored.

The secondary endpoints in the study included confirmed ORR assessed by the independent central review (IRC), investigator, duration of response (DoR), intracranial central nervous system (CNS) ORR (IRC-assessed), intracranial CNS progression-free survival (PFS), disease control rate (DCR), time to response, time on treatment, and overall survival (OS).

The primary analysis of ORR is based on estimated response rate and its corresponding confidence interval. FDA traditionally uses ORR assessed by IRC as the primary analysis and assessment by the investigators as secondary. In this review, both assessment methods will be evaluated.

Sample Size

There were no formal statistical hypotheses specified for Study AP26113-13-201. Study AP26113-13-201 was designed to determine the efficacy in patients treated with daily oral administration of brigatinib (AP26113) tablets at a dose of 90 mg QD continuously or 90 mg QD for 7 days followed by escalation to 180 mg QD continuously. The primary analysis of ORR, in the intention-to-treat (ITT) population was computation of exact 2-sided 97.5% binomial confidence intervals for each treatment arm. The study was designed to detect an ORR of 35%, given that an uninteresting ORR of 20%. A sample size of at least 218 patients (109 per arm) was determined to provide approximately 88% power to rule out an uninteresting rate of 20% when the true rate was 35% or higher, with a two-sided alpha of 0.025 using an exact binomial

test. The treatment regimen was considered to have achieved the primary objective when the ORR (investigator assessed) was shown to be significantly higher than 20% at a two-sided alpha level of 0.025 at final analysis for the given regimen.

FDA usually considers a 95% CI in the evaluation of ORR for single arm trials without adjusting the level of confidence. Thus, the 95% CI will be reported in this review.

The point estimate for ORR was calculated as the proportion of the randomized patients who are confirmed to have achieved CR or PR after the initiation of study treatment using the following formula: ORR = (#confirmed Investigator-based CR or PR)/(#Randomized patients)*100%. The 95% confidence intervals were based on the 95% Clopper-Pearson type exact binomial confidence intervals.

FDA's review of efficacy was limited to the analysis of ORR and corresponding DoR, based on investigator and IRC assessments. The clinical data-cutoff dates were February 29, 2016, for the investigator-assessed results and May 31, 2016, for the IRC-assessed results.

Intracranial CNS ORR

Intracranial CNS ORR (IORR) was evaluated by contrast-enhanced brain magnetic resonance imaging (MRI) scans and analyzed by neuroradiologists in an IRC. The reviewers were blinded to investigator assessment and treatment assignment. Up to 5 measurable brain metastases could be chosen as target lesions by the independent reviewers. Response in patients with at least 1 measurable brain lesion ($\geq$10 mm) was defined as a $\geq$30% decrease in the sum of the longest diameters of target lesions and nonprogression in non-target lesions. Response in patients with only nonmeasurable brain metastases was defined as disappearance of all lesions (complete response).

For patients with brain metastases at baseline, all intracranial efficacy assessments were based on IRC assessments, including:

- Confirmed intracranial ORR per a modification of RECIST v1.1 (confirmed by 2 scans 4 weeks apart)
- Intracranial PFS
- Intracranial duration of response.
- An additional IRC assessment was performed to assess efficacy endpoints in the intracranial CNS in randomized patients with active brain metastases assessed by MRI at enrollment. For randomized patients with active brain metastases at enrollment, intracranial CNS ORR was defined as the proportion of the patients who have achieved CR or PR in the intracranial CNS per a modification of RECIST v1.1 as evaluated by IRC after the initiation of study treatment.

For patients with active brain metastases in the intracranial CNS at enrollment, intracranial CNS ORR (PD, SD, PR, CR) was determined by restricting the RECIST v1.1 criteria to lesions in the intracranial CNS only (target, non-target, and new lesions). A new lesion in the intracranial CNS

was scored as PD in the intracranial CNS. If a patient progresses due to lesions outside the intracranial CNS and continues on study treatment, the patient will continue to be evaluated as SD, PR, or CR in the intracranial CNS until disease progression in the intracranial CNS or the patient discontinues study treatment. Confirmation of CR or PR was performed 4 weeks (allowing a minus 3-day window) or more after initial response.

Intracranial CNS ORR assessed by the IRC and the exact 2-sided 95% binomial confidence intervals were calculated; median intracranial CNS PFS was estimated using the Kaplan-Meier method. The formulas for intracranial CNS ORR were calculated as follows: intracranial CNS ORR per IRC = (#IRC-assessed confirmed intracranial CNS CR or PR) / (#Randomized patients with active brain metastasis)*100%.

DOR

The analysis of response duration was based on disease assessments by the investigator and IRC using the progression and censoring scheme for PFS shown in Table 25. Duration of response (DoR) was calculated as the time from the date of first response until disease progression.

Table 25: Schema for Progression and Censoring PFS

#Rule	Situation	Date of progression or censoring	Outcome
1	Patient randomized but untreated due to death or any other reason		Censored, PFS=1 day
2	No baseline disease assessment		Censored , PFS=1 day
3	No measurable disease at baseline	Date of new lesion(s) or substantial worsening in non- target disease Date of last adequate progression-free radiographic assessment	Progressed Censored
4	No progression or death	Date of last radiological assessment of measured lesions	Censored
5	Death before first PD assessment	Date of death	Progressed
6	Death between adequate assessment visits	Date of death	Progressed
7	Death after one missed radiographic assessment	Date of death	Progressed
8	Death after two of more missed radiographic assessments	Date of last adequate radiographic assessment	Censored
9	Treatment discontinuation prior to documented disease progression or death	Date of last adequate radiographic assessment	Censored
10	New anticancer treatment started without documented disease progression and lead to treatment discontinuation	Date of last adequate progression-free radiographic assessment prior to initiation of new anticancer treatment	Censored
11	Cancer-related surgery prior to documented disease progression	Date of last adequate progression-free radiographic assessment prior to surgery	Censored
12	Disease progression documented between scheduled visits	Earliest of the following: Date of radiological assessment showing new lesion (if progression is based on new lesion); Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)	Progressed
13	Disease progression after 1 missed follow-up disease assessment	Date of progression	Progressed
14	Disease progression after 2 or more missed follow-up disease assessments (death at any time)	Date of last adequate progression-free radiographic assessment	Censored

Source: SAP Table 2

Analysis sets

Per the final SAP, the primary efficacy analysis population was limited to the intent-to-treat (ITT) population, which included all patients randomized to each regimen regardless of whether they received study drug or adhered to the assigned dose.

Additional sensitivity analyses of the primary endpoint and selected secondary efficacy endpoints were performed using the per-protocol population. The per-protocol population excluded all patients in the treated population that did not meet key entry criteria, had no measurable disease at baseline, or have no adequate post-baseline radiographic response assessment. In cases of discrepant results in the per-protocol population between investigator and IRC results, analysis of the ORR was performed for both assessments.

Protocol Amendments

The SAP was amended on July 22, 2016 and on August 4, 2016. Amendment V2.0 added documentation for resolution of QC findings that required information not already contained in existing references. Amendment V3.0 added definitions for bradycardia and tachycardia heart rate values.

7.2.2. AP26113-11-101

AP26113-11-101 is a single arm, open-label, multicenter, dose-finding and cohort expansion study designed to evaluate the safety and tolerability, pharmacokinetics and preliminary anti-tumor activity of brigatinib. A total of 137 patients were enrolled, 66 in the dose-escalation portion and 71 into one of five expansion cohorts:

- NSCLC patients with ALK rearrangements naive to prior ALK inhibitor therapy (n=4);
- NSCLC patients with ALK rearrangements resistant to at least one prior ALK inhibitor (n=42);
- NSCLC patients with EGFR activating mutations resistant to at least one prior EGFR inhibitor (n=1);
- Patients with any cancers with abnormalities in ALK or other targets against which AP26113 may have activity (n=18); and
- NSCLC patients with ALK rearrangements who were either naïve or resistant to crizotinib and who had active brain metastases (n=6).

Patients were assigned to one of 11 dosing regimens of brigatinib and treatment continued until disease progression or other stopping criteria were met. Two RP2Ds were selected (90 mg daily and 90 mg daily for 7 days followed by 180 mg daily).

The primary endpoint of the dose escalation portion was to determine the recommended phase 2 dose of AP26113 and secondary endpoints included maximum tolerated dose, safety and tolerability, and plasma PK parameters. In the cohort expansion portion of the study, the

primary endpoint was overall response rate by RECIST, and secondary endpoints were safety and tolerability, plasma PK, and efficacy assessments including PFS, TTP, and OS. For the cohort of patients with intracranial metastases, the primary endpoint was CNS response by RECIST.

7.2.3. Study Results

Compliance with Good Clinical Practices

The Applicant stated in the NDA clinical study report for Trial ALTA that the study was conducted in accordance with:

- The Declaration of Helsinki;
- The International Conference on Harmonisation (ICH);
- Good Clinical Practices; and
- FDA regulations (21 Code of Federal Regulations [CFR] Parts 50 and 56) for the protection of the rights and welfare of human patients participating in biomedical research.

Financial Disclosure

The Applicant submitted a list of investigators (NDA Module 1.3.4) and FDA forms 3454 and 3455. The Applicant appeared to adequately disclose the financial interests/arrangements of clinical investigators. The financial disclosure data does not raise questions about the integrity of the data. See Appendix 13.2 of this review for details of financial disclosure information.

Patient Disposition

Of the 222 patients enrolled in Study AP26113-13-201, three patients were not treated in Arm A. Two patients were not treated due to serious adverse events prior to the first dose of study drug and one patient withdrew consent to participate prior to the first dose of study drug. The median duration of follow-up was 7.97 months for the 222 enrolled patients.
Table 26 summarizes patient disposition as of the data extraction date of February 29, 2016.

Table 26: Patient Disposition

Disposition	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)
Discontinued Patients, n (%)	45 (40.2)	34 (30.9)	79 (35.6)
Ongoing Patients, n (%)	64 (57.1)	76 (69.1)	140 (63.1)
Primary Reason for Treatment Discontinuation n (%)	29 (25.9)	16 (14.5)	45 (20.3)
Clinical Progressive Disease, n (%)	4 (3.6)	3 (2.7)	7 (3.2)
Adverse Event, n (%)	3 (2.7)	9 (8.2)	12 (5.4)
Death, n (%)	7 (6.3)	1 (0.9)	8 (3.6)
Non-compliance with study drug, n (%)	0	1 (0.9)	1 (0.5)
Withdrawal by patient, n (%)	2 (1.8)	4 (3.6)	6 (2.7)
Follow-up (months)			
N	112	110	222
Mean (SD)	7.97 (4.078)	8.91 (3.984)	8.43 (4.050)
Median	7.75	8.26	7.97
Min, Max	0.1, 16.7	0.1, 20.2	0.1, 20.2

Source Clinical Study Report Table 10-1

Protocol Violations/Deviations

The Applicant described 803 protocol deviations for Trial ALTA as of the database lock, most of which were minor and had no impact on safety or efficacy. There were 37 (4.6%) deviations that were considered major, and the Applicant determined that these major deviations did not impact the interpretation of study results. Deviations involving eligibility criteria included enrollment of a patient with meningeal lesions, enrollment of a patient with radiographic evidence of spinal cord compression, and enrollment of 3 patients with lab values outside of the range for eligibility (one each for hemoglobin, amylase, and lipase). Additionally, seven patients had protocol deviations noted where a prohibited concomitant medication was administered. In the opinion of the clinical reviewer, these deviations are unlikely to impact the interpretation of the efficacy and safety results.

In AP26113-11-101, there was one patient removed from the study for a protocol violation in which the patient was taking another anti–tumor agent at the time of starting brigatinib and the patient received only one dose of brigatinib. Protocol deviations involving eligibility criteria included enrollment of 5 patients who received erlotinib or an investigational agent within 14 days of brigatinib, 3 patients with leptomeningeal disease, and 3 patients with no measurable disease. As with Trial ALTA, the clinical reviewer determined that the deviations are unlikely to impact the interpretation of the efficacy and safety results.

Table of Demographic Characteristics

The demographics of the enrolled population are summarized in Table 27.

Table 27: Summary of Demographics

Demographics	Arm A 90 mg QD N=112	Arm B 90 mg QD →180 mg QD N=110	Total N=222
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 (SD)	51 5 (13 01)	55 5 (12 96)	53 4 (13 11)
Median	50 5	56 5	54
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: Clinical Study Report Table 10-2

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

A summary of the major baseline characteristics is provided in Table 28. In Table 28, subjects with a best response to prior crizotinib regimen of "Other" include two patients for whom a response of PR or CR was achieved but the exact classification was unknown.

Table 28: Summary of Major Baseline Characteristics

	Arm A 90 mg QD N=112	Arm B 90 mg QD →180 mg QD N=110	Total Patients N=222
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)
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)			
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
Brain Metastases at Study Entry, n (%)	80 (71 4)	74 (67 3)	154 (69 4)
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	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)
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: Clinical Study Report Table 10-3

Efficacy Results – Primary Endpoint

The data-cutoff date for the submitted Clinical Study Report (CSR) was February 29, 2016, for the investigator-assessed results and May 31, 2016, for the IRC-assessed results. Table 29 provides the investigator-assessed and IRC-assessed confirmed objective response rate along with the respective durations of response.

Table 29: Results of Response and Duration of Response

	Investigator-assessed			IRC-assessed		
Efficacy Parameter	**Arm A 90mg QD N=112**	**Arm B 90mg QD → 180 mg QD N=110**	**Total N=222**	**Arm A 90mg QD N=112**	**Arm B 90mg QD → 180 mg QD N=110**	**Total N=222**
Confirmed ORR						
n(%)	50 (44.6)	59 (53.6)	109 (49.1)	54 (48.2)	58 (52.7)	112 (50.5)
95% CI	35.2, 54.3	43.9, 63.2	42.4, 55.9	38.7, 57.9	43.0, 62.3	43.7, 57.2
CR	1 (0.9)	4 (3.6)	5 (2.3)	4 (3.6)	5 (4.5)	9 (4.1)
PR	49 (43.8)	55 (50.0)	104 (46.8)	50 (44.6)	53 (48.2)	103 (46.4)
Duration of Response						
Median	13.8	11.1	13.8	13.8	13.8	13.8
95% CI	5.6, 13.8	9.2, 13.8	9.9, 13.8	7.4, NE	9.3, NE	9.3, NE

NE= Not Estimable
Source: Adapted from CSR Tables 11-1, 14.2.1.2, and 14.2.6.2

The Applicant provided the exact 97.5% confidence interval (CI) for the investigator confirmed ORR as pre-specified in the statistical analysis plan. Since 95% CIs are the standard in evaluating single arm studies, 95% CIs were computed based on investigator and IRC-confirmed ORR results.

Based on investigator-assessment, confirmed ORR was 44.6% (95% CI: 35.2, 54.3) and 53.6% (95% CI: 43.9, 63.2) in Arms A and B, respectively. Median DoRs were 13.8 (95% CI: 5.6, 13.8) months and 11.1 (95% CI: 9.2, 13.8) months in Arms A and B, respectively.

Based on the IRC-assessment, confirmed ORR was 48.2% (95% CI: 38.7, 57.9) and 52.7% (95% CI: 43.0, 62.3) in Arms A and B, respectively. Median DoRs were 13.8 (95% CI: 7.4, NE) months and 13.8 (95% CI: 9.3, NE) months in Arms A and B, respectively.

Note that duration of response was based on responders that had dates of first confirmatory CR/PR and corresponding dates of first PD before data-cutoff. Investigator-assessed DoR was based on 14/50 responders in Arm A and 12/59 responders in Arm B. IRC-assessed DoR was based on 17/54 responders in Arm A and 14/58 responders in Arm B.

As a sensitivity analysis, the primary analyses for ORR was conducted on the per-protocol population (190 patients total; 97 in Arm A and 93 in Arm B). The investigator-confirmed ORR was 47.4% (95% CI: 37.2, 57.8) for patients in Arm A and 59.1% (95% CI: 48.5, 69.2) for patients in Arm B.

A sensitivity analysis of ORR assessed by investigator on the ITT population on all responses including unconfirmed responses was stated in the SAP but was never presented in the clinical study report. The statistical reviewer was able to produce the results based on the analysis dataset. The investigator-confirmed ORR was 46.4% (95% CI: 37, 56) for patients in Arm A and 55.5% (95% CI: 45.7, 64.9) for patients in Arm B, as shown in Table 30.

Table 30: Sensitivity Analysis with Unconfirmed Responses

	Investigator-assessed with unconfirmed responses		
Efficacy Parameter	**Arm A 90mg QD N=112**	**Arm B 90mg QD → 180 mg QD N=110**	**Total N=222**
Confirmed ORR			
n(%)	52 (46.4)	61 (55.5)	113 (50.9)
95% CI	37, 56	45.7, 64.9	44.1, 57.7
Confirmed CR	1 (0.89)	4 (3.64)	5 (2.25)
Confirmed PR	49 (43.75)	55 (50.0)	104 (46.85)
Unconfirmed PR	2 (1.79)	2 (1.82)	4 (1.80)

Efficacy Results – Secondary and other relevant endpoints

Of the 222 patients in the ITT population, 217 patients had baseline MRI scans of the brain read by IRC, and 153 patients had brain metastases identified by IRC at baseline (44 patients with measurable lesions and 109 patients with only non-measureable lesions at baseline). Of the patients with measurable lesions, 34 patients had at least 1 active brain metastasis at baseline identified by the investigator and for those with non-measureable lesions, there were 68 patients who had a least 1 active brain metastasis at baseline. An active brain metastasis was defined as a lesion that has not previously been irradiated or had prior radiation treatment but then definitely progressed after being irradiated, as assessed by the investigator.

Table 31: IRC-Assessed Intracranial ORR in Patients with Brain Metastases at Baseline

	Patients with Measurable Brain Metastases			Patients with Only Nonmeasurable Brain Metastases		
Efficacy Parameter	**Arm A 90mg QD N=26**	**Arm B 90mg QD → 180 mg QD N=18**	**Total N=44**	**Arm A 90mg QD N=54**	**Arm B 90mg QD → 180 mg QD N=55**	**Total N=109**
Confirmed IORR						
n(%)	11 (42.3)	12 (66.7)	23 (52.3)	4 (7.4)	10 (18.2)	14 (12.8)
95% CI	23.4, 63.1	41.0, 86.7	36.7, 67.5	2.1, 17.9	9.1, 30.9	7.2, 20.6
CR	2 (7.7)	0	2 (4.5)	4 (7.4)	10 (18.2)	14 (12.8)
PR	9 (34.6)	12 (66.7)	21 (47.7)	NA	NA	NA
Duration of Response						
Median	NE	5.6	5.6	NE	NE	NE
95% CI	3.7, NE	3.7, NE	3.9, NE	NE, NE	9.3, NE	9.3, NE

NE= Not Estimable
Source: Adapted from CSR Table 11-2

Table 31 presents the IRC-confirmed ORR by measurability status in patients with brain metastasis at baseline. The IRC-confirmed ORRs in patients with measurable brain metastases at baseline were 42.3% (95% CI: 23.4, 63.1) and 66.7% (95% CI: 41, 86.7) in Arms A and B, respectively. Median DoRs for Arms A and B were not estimable and 5.6 (95% CI: 3.7, not estimable) months, respectively. For patients with non-measurable brain metastases at baseline, the IRC-confirmed ORRs were 7.4% (95% CI: 2.1, 17.9) and 18.2% (95% CI: 9.1, 30.9) in Arms A and B, respectively. Respective DoRs were not estimable in either arm.

Table 32: IRC-Assessed Intracranial ORR IN Patients with Active Brain Metastases at Baseline

	Patients with Measurable Active Brain Metastases			Patients with Only Nonmeasureable Active Brain Metastases		
Efficacy Parameter	**Arm A 90mg QD N=19**	**Arm B 90mg QD → 180 mg QD N=15**	**Total N=34**	**Arm A 90mg QD N=32**	**Arm B 90mg QD → 180 mg QD N=36**	**Total N=68**
Confirmed IORR						
n(%)	8 (42 1)	11 (73 3)	19 (55 9)	3 (9 4)	7 (19 4)	10 (14 7)
95% CI	20 3, 66 5	44 9, 92 2	37 9, 72 8	2 0, 25 0	8 2, 36 0	7 3, 25 4
CR	2 (10 5)	0	2 (5 9)	3 (9 4)	7 (19 4)	10 (14 7)
PR	6 (31 6)	11 (73 3)	17 (50 0)	NE	NE	NE
Duration of Response						
Median	NE	5 6	NE	NE	NE	NE
95% CI	3 7, NE	3 0, NE	3 7, NE	NE	9 3, NE	9 3, NE

NE= Not Estimable
Source: Adapted from CSR Tables 11-3, 14.2.5.2, 14.2.5.11

Table 32 presents the IRC-confirmed ORR by measurability status in patients with *active* brain metastasis at baseline. The investigator-confirmed ORRs in patients with *active* measurable brain metastases at baseline were 42.1% (95% CI: 20.3, 66.5) and 73.3% (95% CI: 44.9, 92.2) in Arms A and B, respectively. Respective median DoRs were not estimable and 5.6 (95% CI: 3.0,

not estimable) months in Arms A and B. For patients with non-measurable active brain metastases at baseline, the IRC-confirmed ORRs were 9.4% (95% CI: 2.0, 25.0) and 19.4% (95% CI: 8.2, 36) in Arms A and B, respectively. Respective DoRs were not estimable in either arm.

Table 33 presents a summary of confirmed ORR and median DoR results for six specific subgroups. Table 33a provides the investigator-confirmed ORR results by age category (Age 18-64 years vs. Age≥65 years). Table 33b provides the investigator-confirmed ORR results by sex (Females vs. Males). Table 33c provides the investigator-confirmed ORR results by race category (Asian vs. Non-Asian). Table 33d provides the investigator-confirmed ORR for patients with best response to prior crizotinib (best response of CR or PR vs. best response of other or unknown). Table 33e provides the investigator-confirmed ORR results by prior chemotherapy status (Prior Chemotherapy vs. No Prior Chemotherapy). The statistical reviewer calculated the IRC-confirmed ORR results by region (North America vs. Non- North America), presented in Table 33f. Results in Table 33 are compared to IRC-assessed ORR and DoR results from the overall population in Table 29.

Age

The investigator-confirmed ORR and median DoR results in the patients aged 18 to 64 years was similar to the IRC-confirmed ORR and median DoR in the overall population. For patients aged greater than or equal 65 years, the investigator-confirmed ORR was similar to the IRC-confirmed ORR in the overall population. For patients greater than or equal to 65 years of age in Arm A, the median DoR was less than the IRC-confirmed median DoR in the overall population.

Sex

The investigator-confirmed ORR results in females and males were similar to the IRC-confirmed ORR results in overall population. Median DoR was similar to the IRC-confirmed median DoR in the overall population, except for females in Arm B and males in Arm A where the median DoR was not estimable.

Race

T the investigator-confirmed ORR and median DoR results in Asians and Non-Asians were similar to the IRC-confirmed results in the overall population. Median DoR was similar to the IRC-confirmed median DoR in the overall population, except for Non-Asians in Arm A where median DoR was not estimable.

Best response to Prior Crizotinib

The investigator-confirmed ORR and median DoR for patients with best response to prior crizotinib of CR or PR were similar to the IRC-confirmed results in the overall population. For subjects with best response of other or unknown, the investigator-confirmed ORR was less than the IRC-confirmed ORR in the overall population. For subjects with best response of other or

unknown, median DoR was less than and was similar to the IRC-confirmed median DoR of the overall population in Arms A and B, respectively.

Prior Chemotherapy

The investigator-confirmed ORRs for patients with prior chemotherapy and with no prior chemotherapy were similar to the IRC-confirmed ORR in the overall population. For patients with prior chemotherapy, median DoR was not estimable in Arm A and median DoR in Arm B was similar to IRC-confirmed median DoR in the overall population. For patients with no prior chemotherapy, median DoR was lower for both Arms A and B compared to the IRC-confirmed median DoR in the overall population.

Region

The IRC-confirmed ORRs for patients from North American sites and those from non-North American sites were similar to the IRC-confirmed ORR in the overall population. However, subjects in Arm A from North American sites had an ORR that was slightly less than the IRC-confirmed ORR in Arm A in the overall population. For patients from North American sites, median DoR was not estimable in Arm B and median DoR in Arm A was less than the IRC-confirmed median DoR in Arm A in the overall population. For patients from non-North American sites, median DoR in Arm A was similar the IRC-confirmed median DoR in Arm A in the overall population and median DoR in Arm B was less than the IRC-confirmed median DoR in Arm B in the overall population. Note that Table 33 shows that there were no outlier subgroups that were observed. However, the subgroup analyses were exploratory and sample sizes were small, which precludes reaching any conclusions regarding ORR or DoR.

Table 33: Response Rates In Subgroups

a.)

	Age 18–64 Years			Age ≥65 Years		
Efficacy Parameter	Arm A N=90	Arm B N=80	Total N=170	Arm A N=22	Arm B N=30	Total N=52
Confirmed ORR						
n(%)	37 (41.1)	44 (55.0)	81 (47.6)	13 (59.1)	15 (50.0)	28 (53.8)
95% CI	30.8, 52.0	43.5, 66.2	39.9, 55.4	36.4, 79.3	31.3, 68.7	39.5, 67.8
Duration of Response						
Median	13.8	11.1	13.8	7.4	13.8	13.8
95% CI	5.6, 13.8	9.2, NE	9.2, 13.8	3.7, NE	3.9, 13.8	5.6, 13.8

b.)

	Female			Male		
Efficacy Parameter	Arm A N=62	Arm B N=64	Total N=126	Arm A N=50	Arm B N=46	Total N=96
Confirmed ORR						
n(%)	27 (43.5)	37 (57.8)	64 (50.8)	23 (46.0)	22 (47.8)	45 (46.9)
95% CI	31.0, 56.7	44.8, 70.1	41.7, 59.8	31.8, 60.7	32.9, 63.1	36.6, 57.3
Duration of Response						
Median	13.8	NE	13.8	NE	13.8	13.8
95% CI	5.6, 13.8	9.2, NE	9.9, 13.8	5.6, NE	7.2, 13.8	5.6, 13.8

c.)

	Asian			Non-Asian		
Efficacy Parameter	Arm A N=39	Arm B N=30	Total N=69	Arm A N=73	Arm B N=80	Total N=153
Confirmed ORR						
n(%)	18 (46.2)	18 (60.0)	36 (52.2)	32 (43.8)	41 (51.3)	73 (47.7)
95% CI	30.1, 62.8	40.6, 77.3	39.8, 64.4	32.2, 55.9	39.8, 62.6	39.6, 55.9
Duration of Response						
Median	13.8	13.8	13.8	NE	11.1	NE
95% CI	5.6, 13.8	7.2, 13.8	7.0, 13.8	5.6, NE	9.2, NE	9.2, NE

d.)

	Best Response of CR/PR			Best Response of Other or Unknown		
Efficacy Parameter	Arm A N=71	Arm B N=73	Total N=144	Arm A N=41	Arm B N=37	Total N=78
Confirmed ORR						
n(%)	36 (50.7)	47 (64.4)	83 (57.6)	14 (34.1)	12 (32.4)	26 (33.3)
95% CI	38.6, 62.8	52.3, 75.3	49.1, 65.8	20.1, 50.6	18.0. 49.8	23.1, 44.9
Duration of Response						
Median	13.8	13.8	13.8	5.6	11.1	11.1
95% CI	7.4, 13.8	7.4, 13.8	9.2, 13.8	3.7, NE	11.1, NE	5.6, NE

e.)

	Prior Chemotherapy			No Prior Chemotherapy		
Efficacy Parameter	Arm A N=83	Arm B N=81	Total N=164	Arm A N=29	Arm B N=29	Total N=58
Confirmed ORR						
n(%)	35 (42.2)	44 (54.3)	79 (48.2)	15 (51.7)	15 (51.7)	30 (51.7)
95% CI	31.4, 53.5	42.9, 65.4	40.3, 56.1	32.5, 70.6	32.5, 70.6	38.2, 65.0
Duration of Response						
Median	NE	11.1	NE	7.4	7.2	7.4
95% CI	5.6, NE	9.2, NE	9.9, NE	5.6, 13.8	3.7, 13.8	5.6, 13.8

f.)

	North America			Non-North America		
Efficacy Parameter	Arm A N=23	Arm B N=26	Total N=49	Arm A N=89	Arm B N=84	Total N=173
Confirmed ORR						
n(%)	8 (34.8)	12 (46.2)	20 (40.8)	46 (51.7)	46 (54.8)	92 (53.2)
95% CI	16.4, 57.3	26.6, 66.6	27, 55.8	40.8, 62.4	43.5, 65.7	45.5, 60.8
Duration of Response						
Median	7.3	NE	NE	13.8	9.7	13.8
95% CI	5.6, NE	NE, NE	5.6, NE	7.4, NE	7.5, NE	7.5, NE

NE = Not Estimable
Source Adapted from CSR Tables 11-4 11-5 11-6 11-8 11-9

7.3. Integrated Review of Effectiveness

Because only Trial ALTA supported the efficacy claim, no integrated review of effectiveness was performed. As such, all subsections have been deleted.

7.4. Review of Safety

7.4.1. Safety Review Approach

The clinical review of adverse events of brigatinib in patients with ALK+ NSCLC primarily focused on evaluation of Arm B of Trial ALTA, an open-label, multicenter trial in which patients were randomized (1:1) to one of two doses of brigatinib. In Trial ALTA, of the 222 subjects randomized, 219 received at least one dose of any study treatment. One-hundred nine (109) patients in Arm A received brigatinib at a dose of 90 mg daily orally, and 110 patients in Arm B received brigatinib at a dose of 90 mg daily for 7 days, then 180 mg daily orally. Three patients in Arm A were randomized but never treated. The safety monitoring period started at the time of informed consent signature and lasted for 30 days following discontinuation of treatment for all adverse events (AEs) or related serious AEs (SAEs). Data from patients enrolled in AP26113-11-101, the dose escalation and cohort expansion study, supported the safety review. Data from AP26113-11-101 and ALTA were not pooled because different doses were used. No additional safety signals were identified based on review of data from AP26113-11-101.

7.4.2. Review of the Safety Database

Overall Exposure

In ALTA, 110 patients in Arm B received brigatinib at a dose of 90 mg daily for 7 days then 180 mg daily. The median duration of exposure to brigatinib in Arm B was 10.7 months (range 0.07-23.6) at the time of data cut-off for the 60-day Safety Update Report (31 May 2016).

Table 34: Exposure for Trial ALTA (Reviewer Table)

	Arm A 90 mg regimen (N=112)	Arm B (n=110) 180 mg regimen[1] (N=110)
Duration of exposure in months		
Median	9.8	10.7
Range	(0.3-20)	(0.07-23.6)
Duration of exposure n (%)		
Less than 3 months	22 (20.2)	15 (15.7)
3- <6 months	9 (8.3)	12 (10.9)
6- <12 months	42 (38.5)	42 (38.2)
≥ 12 months	36 (33)	41 (37.3)
Relative Dose intensity (%)[2]		
Median	100	99.5

Range	(65-192)	(33-101)

[1] The 180 mg regimen includes dosing at 90 mg daily for 7 days prior to escalation to 180 mg daily.
[2] 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.

Relevant characteristics of the safety population:

Table 35: Patient Characteristics for the ITT Population (Reviewer Table)[1]

	Arm A 90 mg regimen (n=112)	**Arm B 180 mg regimen[1] (n=110)**
Age (years)		
Mean (SD)[2]	52 (13)	56 (13)
Median	51	57
Range	18-82	20-81
≥ 65 years n (%)	22 (20)	30 (27)
Race n (%)		
White	72 (64)	76 (69)
Asian	39 (35.)	30 (27)
Other/Unknown	0	4 (3.6)
Gender n (%)		
Female	62 (55)	64 (58)
Male	50 (45)	46 (42)
ECOG Performance Status n (%)		
0	34 (30)	45 (41)
1	71 (63)	56 (51)
2	7 (6)	9 (8)
Smoking Status n (%)		
Never-smoker	71 (63)	63 (57)
Past smoker	34 (30)	43 (39)
Active smoker	6 (5)	4 (4)

[1] The 180 mg regimen includes dosing at 90 mg daily for 7 days prior to escalation to 180 mg daily.
[2] SD standard deviation

Table 36: Baseline Disease Characteristics for the ITT Population (Reviewer Table)[1]

	Arm A 90 mg regimen (N=112) n (%)	Arm B (n=110) 180 mg regimen[2] (N=110) n (%)
ALK+ by Vysis FISH n (%)		
Yes	100 (89)	98 (89)
No[3]	12 (11)	12 (11)
Stage n (%)		
IIIA	0	1 (0.9)
IIIB	3 (2.7)	1 (0.9)
IV	109 (97)	108 (98)
Histology n (%)		
Adenocarcinoma	107 (96)	108 (98)
Adenosquamous	1 (0.9)	0
Squamous	2 (1.8)	1 (0.9)
Other[4]	2 (1.8)	1 (0.9)
CNS Metastases at Baseline n (%)	80 (71)	74 (67)
Prior Platinum-based Chemotherapy n (%)	83 (74)	80 (73)
Prior Systemic Therapy (including crizotinib) n (%)		
1 regimen (includes crizotinib)	29 (26)	27 (25)
2 regimens (includes crizotinib)	40 (35.7)	45 (41)
≥ 3 regimens (includes crizotinib)	43 (38)	38 (35)
Prior radiotherapy n (%)		
Prior radiotherapy (to any site)	68 (61)	58 (53)
Radiotherapy for brain metastasis	50 (45)	45 (41)
Most Recent Systemic Therapy was crizotinib n (%)	107 (96)	106 (96)
Complete Response	5 (4.5)	2 (1.8)
Partial Response	65 (58)	70 (64)
Stable Disease	28 (25.)	21 (19)
Progressive Disease	8 (7)	6 (5.5)
Other/Unknown[5]	6 (5.4)	11 (10)

[1] ITT population contains 3 patients who are not included in the safety population in Arm A because they did not receive therapy.

[2] The 180 mg regimen includes dosing at 90 mg daily for 7 days prior to escalation to 180 mg daily.

[3] Of the 24 patients without a positive local or central ALK Vysis FISH (versus a different) test result, no central test result was listed due to insufficient tissue (n=6); improper tissue preparation (n=12); or central test negative (n=5); central test abnormal – loss of 3' ALK signal (n=1).

[4] Large cell and mucoepidermoid carcinoma

[5] "Other" denotes 2 patients (one in each arm) for whom PR or better was achieved but unable to classify as PR or CR. "Unknown" denotes the remaining patients for whom the best response to crizotinib was unavailable. Of note, all patients ultimately had progression of disease on crizotinib prior to enrollment.

Adequacy of the safety database:

The safety data from these two trials is adequate to perform an assessment of safety for this application. Although the overall safety database was limited (based on the number of patients), the population under review in this application has life-threatening lung cancer for which an unmet medical need exists. In general, the safety database appears comparable with the safety databases of alectinib and ceritinib at the time of Accelerated Approval. Additional safety data will be obtained by the Applicant (postmarketing) in the trial intended to support regular approval of brigatinib.

An insufficient number of patients aged 65 years or greater were enrolled into Trial ALTA to permit a substantive safety review of this population.

7.4.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

This submission was of adequate quality for clinical review. There are no concerns regarding the integrity of the submission.

Categorization of Adverse Events

The definitions of AEs and SAEs provided in the protocols were appropriate. The AE collection period for both studies was from the date of start of treatment with brigatinib until 30 days following the last dose of study treatment or until any ongoing AE thought to be at least possibly brigatinib related had resolved to Grade ≤ 1 or baseline. The Applicant used Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0 to map verbatim terms from the CRFs to preferred terms (PTs) to code all AEs reported by the Investigator. The incidence and percentage of patients with at least one occurrence of a PT were included, according to the most severe NCI CTCAE Version 4.0 grade. Verbatim terms in the AEs dataset were analyzed to determine the correctness of the coding of the MedDRA PTs. An analysis of the PT from Trial ALTA adequately represented the verbatim terms.

The Applicant summarized AEs by preferred term. Although the approach was generally appropriate, it led to "splitting" of certain AE terms such "fatigue" and "asthenia" under the preferred terms rather than grouping them together. The potential for splitting was mitigated by the Applicant's use of combined preferred terms, SMQs, or combined HGLTs to define these selected AEs of special interest. Selected AEs were based on grouping AE terms by Standardized MedDRA queries (SMQs) and/or System Organ Classes (SOCs) and included the following:

- Pulmonary Events including early onset pulmonary events and later onset pneumonitis
- Bradycardia
- Hypertension events
- Gastrointestinal events
- Pancreatic events

- Elevated insulin/hyperglycemia events
- Hepatic events
- Skin and subcutaneous tissue events
- Vision disorder events

The safety assessment methods used by the Applicant appeared adequate for the population and indication being investigated.

Routine Clinical Tests

The tests conducted as part of routine clinical testing and the frequency of testing are detailed in the Study Calendars for both trials included in Section 7.2.1 and Section 7.2.2 of this review. Per protocol for both studies, laboratory abnormalities were to be reported as AEs if meeting any of the following criteria:

- Test result is associated with accompanying symptoms that are considered clinically significant in the opinion of the investigator.
- Test result requires additional diagnostic testing (other than merely repeating an abnormal test) or medical/surgical intervention.
- Test result leads to a change in study drug dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
- Test result is considered to be an AE by the investigator or sponsor.

In addition to providing information on laboratory test abnormalities reported as AEs, the Applicant provided laboratory shift tables for clinically relevant laboratory results, with data available for all 219 patients included in the ISS.

The safety assessment methods and time points for routine clinical tests described in the protocols seem adequate for the population and indication being investigated.

7.4.4. Safety Results

Deaths

The Applicant performed an analysis of the cause of death for all patients in Trial ALTA who had died as of the data cut-off date of February 29, 2016, particularly those patients who died within 30 days of the last dose of study drug and those who had a treatment-related adverse event at any time point. A similar analysis was provided for patients in Trial AP26113-11-101 with a cut-off date of November 16, 2015. The Applicant provided detailed narratives of all patient deaths occurring within 30 days for both treatment arms or greater than 30 days if the death was at least possibly treatment-related. This review focuses on Trial ALTA followed by a summary of the ISS.

Trial ALTA
Overall, there were 23 (11%) patients who died within 30 days of the last dose of study drug. No deaths that occurred beyond 30 days were considered by the applicant as possibly related to brigatinib. By arm, there were 16 (15%) deaths in Arm A and 7 (6%) deaths in Arm B. Table 37 summarizes treatment-emergent adverse events leading to death within 30 days of brigatinib by preferred term. In both arms, the primary cause of death was disease progression (9 [8%] in Arm A and 4 [3.6%] in Arm B). Eight patients died for reasons other than disease progression or cancer-related reason for death (e.g., malignant pleural effusion and metastases to meninges).

Table 37: Treatment Emergent Adverse Events Leading to Death within 30 days of Last Dose, Trial ALTA (Reviewer Table)

Reason for Death (PT)	Arm A 90 mg regimen N=109 n (%)	Arm B 180 mg regimen[1] N=110 n (%)	Total N=219 n (%)
Any Death	16 (15%)	6 (6%)	23(11%)
Neoplasm progression	9 (8%)	4 (3.6%)	13 (6%)
Pneumonia	1 (0.9%)	1 (0.9%)	2 (0.9%)
Dyspnea	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%)
Metastases to meninges	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%)

[1] The 180 mg regimen includes dosing at 90 mg daily for 7 days prior to escalation to 180 mg daily.

This clinical reviewer conducted analyses of the 8 narrative summaries in Trial ALTA to assess the cause of death described by the Applicant for all deaths attributed to a TEAE or other deaths that occurred within 30 days of the last dose of study therapy regardless of attribution. The reviewer agreed with the attribution by the Applicant in all but two pneumonia cases: one was pneumonia in a 65 year old man that was determined by the investigator to be unrelated and that the safety reviewer determined was possibly related. The other was pneumonia in a 57 year old woman that was determined by the investigator to be possibly related but that the safety reviewer determined to be unlikely related. The safety reviewer determined that two deaths out of 8, one pneumonia, and one sudden death were possibly be related to brigatinib. Details from the Applicant's narrative summaries for these 8 patients follow:

Pulmonary Embolism
Death due to pulmonary embolism (PE) occurred in a 37 year old man with a history of deep vein thrombosis who was enrolled in Trial ALTA on Arm A receiving brigatinib at 90 mg daily.

On Study Day 191, he was hospitalized for neoplasm progression. The last dose of brigatinib was Day 196. On Day 203, the patient was hospitalized for pulmonary embolism. Due to an oxygenation disorder and suspicion of pneumonia, the patient was started on antibiotics and also received noninvasive ventilation. The patient's respiratory insufficiency worsened, however, and he died on Day 209.

Reviewer comment: Malignancy is associated with venous thrombosis and PE, especially during progression of disease and unlikely caused by brigatinib. Although brigatinib is associated with pulmonary events, in the setting of progressive disease, PE, and pneumonia, it is unlikely that brigatinib was related to this death.

Sudden Death

Sudden death occurred in a 70 year old man with a history of hypercholesterolemia, hypertension, intermittent claudication, and type II diabetes. At the time of enrollment, the patient was experiencing cough, dyspnea, fatigue, and painful respiration. A screening electrocardiogram (ECG) revealed possible left atrial enlargement and a nonspecific T wave abnormality. On Days 1 and 2, the patient took brigatinib 90mg. On Day 3, the patient experienced shortness of breath, diaphoresis, but no chest pain. Upon arrival to the emergency department, he was found to be unresponsive, and despite institution of advanced cardiac life support (ACLS), subsequently died. X-ray showed severe pulmonary edema and left pleural effusion as well as diffuse prominence of the pulmonary interstitium.

Reviewer comment: Despite the patient's risk factors for heart attack and left pleural effusion as risk for dyspnea, the timing of onset of dyspnea is consistent with early onset pulmonary events (EOPE) previously recognized with brigatinib. Insufficient information was available to assess whether this was a cardiac- or pulmonary-related death, so there is a possibility that the patient's death was brigatinib-related.

Pneumonia

Death due to pneumonia occurred in a 57 year old woman 23 days after the last dose of brigatinib at 180 mg daily. She was enrolled to the 180 mg dose level (Arm B) and her last dose of brigatinib was 180 mg. The patient was hospitalized on Study Day 57 for worsening recurrent pneumonia and computed tomography of the chest and abdomen showed slight progression but by RECIST was consistent with stable disease. The patient withdrew consent and the last dose of brigatinib was administered on Day 60. The patient was discharged from the hospital in improved condition, but died on Day 83 due to a separate event of pneumonia.

Reviewer comment: Given that the patient's pulmonary status appeared to improve after discontinuation of brigatinib, but she subsequently died of pneumonia, the death is unlikely related to brigatinib.

A second death attributed to pneumonia took place in a 65 year old man with ongoing dyspnea at the time of enrollment. The patient was enrolled in the 90 mg dose group. On Day 3, he

experienced flu like symptoms, possible fever, headache, productive cough (Grade 2), dyspnea (Grade 2), and nausea. On Day 5, the patient developed hemoptysis. On Day 7, the patient reported increased dyspnea, fever, and deterioration. He was instructed to come to the study site's oncology department immediately, but collapsed and died at home. An autopsy showed widespread dissemination of cancer including lymphangitic carcinomatosis in the right lung, large amounts of tumor tissue in the connective tissue on the left half of the thorax, and growth into epicardial and pericardial fatty tissue. Widespread fibrosis was observed in the left lung and pleura, as well as the pericardium, noted to be an expected finding at autopsy and felt to be the result of antineoplastic effect. Right lung histological changes consistent with diffuse alveolar damage were found, which indicated acute respiratory distress syndrome. The pathologist reported the cause of death as lung cancer, adhesive pericarditis, and respiratory failure. The investigator determined that the cause of death, pneumonia, was not related to brigatinib.

Reviewer comment: Other factors contributed to this patient's death (tumor extension to pericardium and lymphangitic carcinomatosis), but the timing of onset suggests that brigatinib may have been a factor in precipitating the death and therefore is possibly related.

Respiratory failure

A death due to respiratory failure was reported in a 37 year old woman with a history of pulmonary embolism who was enrolled in the 90 mg dose group. On Day 91, the patient complained of upper quadrant pain, dark urine, nausea, acholia with fever, and bilious vomiting, and was hospitalized for the event of acute cholangitis. Her last dose of brigatinib was 90 mg on Day 90, after which brigatinib was interrupted. On Day 105, she was again hospitalized, this time for dyspnea at which times she was found to be hypotensive and oliguric. She died from respiratory failure on Day 106. Computed tomography angiography showed no pulmonary embolism.

Reviewer comment: The relationship between brigatinib and this patient's death could not be excluded, although it seems is unlikely given the preceding hospitalization and complicated clinical course.

Dyspnea

A death due to dyspnea occurred in a 71 year old woman enrolled in the 180 mg dose group. The patient ultimately died following resuscitation of cardiac arrest during a bronchoscopy procedure that was undertaken to treat endobronchial tumor invasion.

Reviewer comment: Given the presence of endobronchial invasion by tumor and her initial improvement with prior removal of the endobronchial "clot," the event of death from dyspnea is not related to brigatinib.

Urosepsis
A death due to urosepsis occurred in a 62 year old woman enrolled in the 90 mg dose group who required multiple hospitalizations for hypdronephrosis and bilateral nephrostomy tubes due to obstruction. She had metastatic disease to the adrenal gland(s), bone, brain, and liver. The patient died on Day 213 of this study.

Reviewer comment: There is no plausible mechanism to suggest that brigatinib led to death by urosepsis, so this death is considered unrelated to brigatinib.

Bacterial meningitis
A death due to bacterial meningitis occurred in a 59 year old woman enrolled in the 90 mg dose group. The patient had brain metastasis at study entry. On Day 71, the patient presented to the emergency department complaining of akathisia, and a peripheral blood culture revealed Listeria monocytogenes. The patient was hospitalized and brigatinib was interrupted (and never restarted). Cerebrospinal fluid was obtained and cytology revealed bacterial meningitis. On Day 74, a brain CT scan revealed post-resuscitation anoxic encephalopathy after the patient received prior cardiopulmonary resuscitation. The patient subsequently received noninvasive supportive care and died on day 89.

Reviewer comment: Listeria monocytogenes is a common cause of bacterial meningitis in cancer patients, including adult patients with cancer (Brouwer, van de Beek, et al. 2006). Given the patient's pre-existing brain metastases and that no plausible mechanism exists for brigatinib to cause bacterial meningitis, the relationship between brigatinib and this death is unlikely.

Summary of Review of Deaths from ISS Database
The Applicant provided an analysis from the ISS database with data from two trials: AP26113-11-101 and Trial ALTA. In AP26113-11-101, 14 patients assigned to the 90 mg dose level and 28 patients assigned to the 180 mg dose level were included in the safety population for analysis.

Overall, 58 of 261 patients (22%) included in the ISS database who received either the 90 mg regimen or the 180 mg regimen died by the time of the data cut-off dates. Deaths were flagged if they occurred within 30 days of brigatinib or if they were assessed as treatment-related regardless of the time of occurrence. There were 18 (15%) deaths at the 90 mg dose level and 9 (6.5%) deaths at the 180 mg dose level. As with Trial ALTA, the majority of deaths were due to disease progression with 10 of 18 (56%) deaths at the 90 mg dose level and 5 of 9 (56%) deaths at the 180 mg dose level. Seventeen deaths in 261 patients (6.5%) were attributed to causes other than disease progression or cancer-related reason for death (e.g., malignant pleural effusion, and metastases to meninges), including 6 (4.9%) at the 90 mg dose level and 12 (8.7%) at the 180 mg dose level. Table 38 summarizes treatment-emergent adverse events leading to death within 30 days of brigatinib or treatment-related deaths at any time by preferred term.

Table 38: Treatment Emergent Adverse Events Leading to Death within 30 days of Last Dose or Treatment-Related, ISS (Reviewer Table)

Reason for Death (PT)	Arm A 90 mg regimen N=123 n (%)	Arm B 180 mg regimen[1] N=138 n (%)	Total N=261 n (%)
Any Death	18 (15%)	9 (6.5%)	27 (21%)
Neoplasm progression	10 (8%)	5 (3.6%)	15 (5.7%)
Pneumonia	1 (0.8%)	1 (0.7%)	2 (0.8%)
Dyspnea	0	1 (0.7%)	1 (0.4%)
Respiratory Failure	1 (0.8%)	0	1 (0.4%)
Sudden death	0	1 (0.7%)	1 (0.4%)
Death	1 (0.8%)	0	1 (0.4%)
Malignant pleural effusion	1 (0.8%)	0	1 (0.4%)
Meningitis bacterial	1 (0.8%)	0	1 (0.4%)
Metastases to meninges	1 (0.8%)	0	1 (0.4%)
Pulmonary embolism	1 (0.8%)	0	1 (0.4%)
Sepsis	0	1 (0.7%)	1 (0.4%)
Urosepsis	1 (0.8%)	0	1 (0.4%)

[1] The 180 mg regimen includes dosing at 90 mg daily for 7 days prior to escalation to 180 mg daily.

Reviewer Comment: In general, additional deaths from the ISS did not provide substantive additional safety information as compared to the data from the ALTA trial. Review of the details of these deaths reveals that respiratory causes, including pneumonia, predominate as a cause of death. Given the absence of a control arm and in a population of lung cancer patients who are predisposed to cardio-pulmonary complications, it is not possible to ascertain with certainty whether brigatinib can cause toxic deaths due in patients with lung cancer.

Serious Adverse Events

Among the 219 patients in ALTA, 85 patients experienced 133 SAEs with similar rates in both arms (38% in Arm A and 40% in Arm B). The three most common SAEs by preferred term in Arm B were pneumonia (7%), pneumonitis (7%), and neoplasm progression (5.5%). In Arm A, neoplasm progression was the most common preferred term (12%) and the rates of pneumonia (2.8%) and pneumonitis (1.8%) were lower than in Arm B. A listing of SAEs by system organ class and preferred term in ≥2 patients by Arm from Trial ALTA is provided in Table 39.

Given the higher number of SAEs in Arm B versus Arm A due to pneumonitis and pneumonia, a separate analysis of these two preferred terms was performed. A total of 21 events occurred in 20 patients (9%) overall in ALTA. Of these, 5 events occurred in Arm A, 4 within 7 days of the first dose. In Arm B, there were 16 events and 8 occurred within 7 days. With regards to other events of special interest, there was one Grade 3 SAE of macular edema in Arm B, but no cases of hypertension, bradycardia, or pancreatitis. Further details of events of special interest can be found in Section 7.4.5.

The analysis of SAEs presented by the Applicant is based on the reporting database and includes randomized patients who reported an AE that met any of the serious criteria, whether or not the event was judged to be related to study drug. Potential drug-relatedness of these SAEs will not be discussed as these reports are from an uncontrolled trial. The definition of SAE according to 21 CFR 312.32(a) is any AEs that result in one of the following outcomes:

- Death
- Life-threatening adverse event
- Initial or prolonged inpatient hospitalization
- Life-threatening adverse event
- Persistent or significant incapacity to perform normal life functions
- Congenital anomaly/birth defect
- Events that may jeopardize the patient and require intervention even in the absence of any of the above criteria

Reference ID: 4090771

Table 39: Treatment-Emergent Serious Adverse Events by Preferred Term in ≥ 2 Patients, Trial ALTA (Reviewer Table)

System Organ Class with Preferred Term	Arm A: 90 mg regimen N= 109		Arm B: 180 mg regimen[1] N=110	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Patients with any SAE	**41 (38)**	**13 (12)**	**44 (40)**	**24 (22)**
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**16**	**2 (1.8)[2]**	**9 (8)**	**2 (1.8)[2]**
Neoplasm Progression	13 (12)	2 (1.8)[2]	6 (5.5)[3]	0
Malignant Pleural Effusion	3 (2.8)	1 (0.9)[2]	3 (2.7)	2 (1.8)[2]
Respiratory, Thoracic, and Mediastinal Disorders	**9 (8)**	**5 (4.6)**	**13 (12)**	**7 (6)[2]**
Pneumonitis	2 (1.8)	2 (1.8)	8 (7)	3 (2.7)[2]
Dyspnea	2 (1.8)	1 (0.9)[2]	2 (2.7)	1 (0.9)[2]
Pulmonary Embolism	2 (1.8)	1 (0.9)[2]	2 (1.8)	1 (0.9)[2]
Infections and Infestations	**8 (7)**	**3 (2.8)**	**11 (10)**	**6 (5.5)[2]**
Pneumonia	3 (2.8)	1 (0.9)[2]	8 (7)	4 (3.6)[2]
Appendicitis	1 (0.9)	1 (0.9)[2]	1 (0.9)	1 (0.9)[2]
Bronchitis	1 (0.9)	0	1 (0.9)	0
Nervous System Disorders	**8 (7)**	**3 (2.8)**	**5 (4.5)**	**2 (1.8)[2]**
Epilepsy	3 (2.8)	1 (0.9)[2]	1 (0.9)	0
General Disorders and Administration Site Conditions	**3 (2.8)**	**2 (1.8)[2]**	**4 (3.6)**	**2 (1.8)[2]**
Device Occlusion	1 (0.9)	0	1 (0.9)	1 (0.9)[2]
General Physical Health Deterioration	1 (0.9)	1 (0.9)[2]	1 (0.9)	0
Musculoskeletal and Connective Tissue Disorders	**4 (3.7)**	**3 (2.8)[2]**	**1 (0.9)**	**1 (0.9)[2]**
Back Pain	1 (0.9)	1 (0.9)[2]	1 (0.9)	1 (0.9)[2]
Injury, Poisoning, and Procedural Complications	**1 (0.9)**	**0**	**5 (4.5)**	**3 (2.7)**
Post Procedural Hemorrhage	0	0	2 (1.8)	1 (0.9)[2]
Ear and Labyrinth Disorders	**2 (1.8)**	**0**	**0**	**0**
Vertigo Positional	2 (1.8)	0	0	0

[1] The 180 mg regimen includes dosing at 90 mg daily for 7 days prior to escalation to 180 mg daily.
[2] There were no Grade 4 events.
[3] This value differs from the Applicant's analysis by one and was obtained by analysis of the safety population from the ADAE.xpt dataset.

Analyses of SAEs from ISS Database
In the ISS database, there was a total of 279 SAEs in 151 of 354 (43%) patients with any grade SAEs at any dose level. In general, the rates and severity of events are similar to those seen for ALTA with no new safety signals identified. With regard to events of special interest, pulmonary toxicity (includes PTs of pneumonia, dyspnea, pneumonitis, and hypoxia) was the most common reason for SAE after neoplasm progression. There were 63 events mapping to one of these PTs out of 279 (23%) in the ISS population. The Applicant also flagged patients with one of the PTs above and from the dataset identified 26 patients out of 354. It is notable that the median time to event occurred on Day 2 of therapy. Grade 3 pancreatitis was reported in 2 patients in AP26113-11-101, one of which occurred in a patient taking 240 mg daily who died of fungal sepsis and the other in a patient on the 180 mg daily dose in the setting of peritoneal carcinomatosis and progression of malignancy. There were no bradycardia or hypertension events. There was one SAE of Grade 3 muscular weakness that occurred in AP26113-11-101, but no other SAEs due to myalgia or rhabdomyolysis were reported. One Grade 3 SAE due to macular edema occurred in a patient from study ALTA as already described above.

Dropouts and/or Discontinuations Due to Adverse Effects

The pre-specified safety withdrawal criteria for both Studies AP26113-11-101 and ALTA were reasonable. A total of 12 (5.5%) patients in the safety population of ALTA discontinued study drug due to an AE. See Table 40 for a list of AEs by preferred term leading to discontinuation of brigatinib.

Table 40: Treatment-Emergent Adverse Events Leading to Treatment Discontinuation by Treatment Arm (Reviewer Table)

Preferred Term	Arm A: 90 mg regimen N=109 n (%)	Arm B: 180 mg regimen[1] N=110 n (%)	Total n=219 n (%)
Patients who discontinued for any AE	**3 (2.8)**	**9 (8.2)**	**12 (5.5)**
Pneumonitis	1 (0.9)	2 (1.8)	3 (1.4)
Pneumonia	0	2 (1.8)	2 (0.9)
Angioedema	0	1 (0.9)	1 (0.5)
Dyspnea	0	1 (0.9)	1 (0.5)
Gastrointestinal Hemorrhage	1 (0.9)	0	1 (0.5)
Malignant Pleural Effusion	1 (0.9)	0	1 (0.5)
Neoplasm Progression	0	1 (0.9)	1 (0.5)
Radiation Pneumonitis	0	1 (0.9)	1 (0.5)
Respiratory Failure	0	1 (0.9)	1 (0.5)

[1] The 180 mg regimen includes dosing at 90 mg daily for 7 days prior to escalation to 180 mg daily.

Analysis of Discontinuations in the ISS Database
In the ISS database, there were a total of 30 of 354 (8.5%) patients who discontinued study therapy due to an AE. The most common reason for discontinuation was pneumonitis (5 patients [1.4%]), pneumonia (3 patients [0.8%]), dyspnea (2 patients [0.6%]), and malignant pericardial effusion (2 patients [0.6%]).

Interruptions
TEAEs that led to dose interruption occurred in 85/219 (39%) patients overall in ALTA. The most common AEs that led to dose interruption in ALTA overall by preferred term were pneumonitis (9 [4.1%]), blood CPK increased (7 [3.2%]), lipase increased (7 [3.2%]), neoplasm progression (6 [2.7%]), and vomiting (6 [2.7%]). The most common AEs that led to dose interruption in Arm A were lipase increased (4 [3.7%]), neoplasm progression (4 [3.7%]), pyrexia (4 [3.7%]), vomiting (3 [2.6%]) and dyspnea (3 [2.6%]). In Arm B the most common AEs that led to dose interruption were pneumonitis (7 [6%]) blood CPK increased (6 [5.5%]), lipase increased (3 [2.7%]), pneumonia (3 [2.7%]), rash erythematous (3 [2.7%]), and vomiting (3 [2.7%]). All dose interruptions due to pneumonitis occurred in the first 7 days on brigatinib 90 mg.

Dose Reductions
TEAEs that led to dose reduction occurred in 30/219 (14%) of patients overall. A greater proportion of patients in Arm B than in Arm A had TEAEs that led to dose reduction (22 [20%] versus 8 [7%], respectively). The only TEAE that occurred in ≥2% of patients overall by preferred term was blood CPK increased (3.2% [7/219]), which occurred in 2 (1.8%) patients in Arm A and 5 (4.5%) patients in Arm B.

Treatment Emergent Adverse Events and Adverse Reactions

At least one TEAE was reported in 216 out of 219 total patients in the safety population from ALTA. The most common TEAEs of any grade occurring in Arm B are nausea, diarrhea, fatigue, cough, and blood creatine phosphokinase increased. Table 41 below summarizes all TEAEs of any grade that occurred in ≥10% of patients or Grade 3-4 TEAEs that occurred in ≥2% of patients.

Table 41: TEAEs Occurring in ≥10% (All Grades) or ≥2% (Grade3-4) of Patients (n=219) in ALTA (Reviewer Table)

Preferred Term[1] Consolidated TEAE Category	Arm A: 90 mg regimen N= 109		Arm B: 180 mg regimen[2] N=110	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Patients with any TEAE	**106 (97)**	**44 (40)**	**110 (100)**	**52 (47)**
Nausea	36 (33)	1 (0.9)[3]	44 (40)	1 (0.9%)[3]
Diarrhea	21 (19)	0	42 (38)	0
Fatigue[4]	32 (29)	2 (1.8)[3]	40 (36)	0
Cough	20 (18)	0	37 (34)	0
Blood Creatine Phosphokinase Increased	12 (11)	3 (2.8)	33 (30)	10 (9)
Headache	30 (28)	0	29 (26)	1 (0.9%)[3]
Vomiting	26 (24)	2 (1.8)[3]	25 (23)	0
Dyspnea	23 (21)	3 (2.8)[3]	23 (21)	1 (0.9%)[3]
Rash[5]	10 (9)	2 (1.8)[3]	23 (21)	4 (3.6)[3]
Hypertension	12 (11)	6 (5.5)[3]	22 (20)	3 (2.7)[3]
Muscle Spasms	13 (12)	0	19 (17)	0
Back pain	11 (10)	2 (1.8)[3]	17 (16)	2 (1.8)[3]
Constipation	21 (19)	1 (0.9)[3]	17 (16)	0
Decreased appetite	24 (22)	1 (0.9)[3]	17 (16)	1 (0.9%)[3]
Aspartate Aminotransferase Increased	9 (8)	1 (0.9)[3]	16 (15)	0
Amylase Increased	9 (8)	1 (0.9)[3]	16 (15)	1 (0.9%)[3]
Arthralgia	15 (14)	1 (0.9)[3]	15 (14)	0
Lipase Increased	8 (7.3)	4 (3.7)	13 (12)	3 (2.7)
Pneumonia	5 (4.6)	2 (1.8)[3]	11 (10)	3 (2.7)[3]
Pneumonitis	3 (2.8)	2 (1.8)	9 (8)	3 (2.7)[3]
Insomnia	12 (11)	0	8 (7)	0
Pyrexia	15 (14)	0	7 (6)	1 (0.9%)[3]
Neutropenia[6]	6 (5.5)	3 (2.8)[3]	6 (5.5)	2 (1.8)[3]
Neoplasm Progression	13 (12)	2 (1.8)[3]	6 (5.5)	0
Pain in Extremity	12 (11)	0	4 (3.6)	1 (0.9%)[3]
Hypoxia	1 (0.9)	0	3 (2.7)	3 (2.7)[3]
Pulmonary Embolism	2 (1.8)	1 (0.9)[3]	3 (2.7)	3 (2.7)[3]
AESI or SMQ				
Interstitial Lung Disease SMQ (narrow)[7]	4	2 (1.8)	10 (9)	3 (2.7)[3]
Bradycardia[8]	6 (5.5)	0	4 (3.6)	0
Hypertension	12 (11)	6 (5.5)	23 (21)	7 (6.3)
Visual Disturbance[9]	4 (3.7)	0	13 (12)	3 (2.7)
Pancreatitis	0	0	0	0
Myalgia[10]	10 (9)	0	18 (16)	1 (0.9)[3]

[1] Patients may have more than one AE per preferred term. A patient is counted once for the most severe event per preferred term.
[2] The 180 mg regimen includes dosing at 90 mg daily for 7 days prior to escalation to 180 mg daily.
[3] There were no Grade 4 events for this preferred term.
[4] The preferred terms fatigue and asthenia were combined.
[5] All preferred terms including the word "rash" were included (e.g. rash macular, rash erythematous, rash pruritic)
[6] The preferred terms neutropenia and neutrophil count decreased were combined.
[7] The preferred terms pneumonitis and interstitial lung disease are represented from Interstitial Lung Disease SMQ narrow.
[8] The preferred terms bradycardia and sinus bradycardia were combined.
[9] The preferred terms visual acuity reduced, vision blurred, diplopia, visual impairment, and macular edema were combined.
[10] The preferred terms myalgia and musculoskeletal pain were combined. There was no preferred term of rhabdomyolysis in the dataset.

Analysis of TEAEs in the ISS database
In the ISS database, a total of 352 of 356 (99%) patients had at least one TEAE. The most common TEAEs were similar to what was observed in Trial ALTA. Table 42 shows the most common TEAEs by preferred term in descending order for the ISS population.

Table 42: TEAE by Preferred Term for the ISS Population (Reviewer Table)

Preferred Term	N=356 ISS Population n (%)
Fatigue[1]	143 (40)
Diarrhea	119 (33)
Nausea	115 (32)
Headache	109 (31)
Cough	105 (29)
Vomiting	85 (24)
Dyspnea	84 (24)
Constipation	74 (21)
Muscle Spasm	58 (16)
Amylase Increased	56 (16)
Hypertension	55 (15)
Abdominal Pain[2]	55 (15)
Rash[3]	55 (15)
Lipase Increased	49 (14)
Blood CPK Increased	45 (13)

[1] The preferred terms fatigue and asthenia were combined.
[2] The preferred terms abdominal pain, upper abdominal pain, and lower abdominal pain were combined.
[3] All preferred terms including the word "rash" were included (e.g. rash macular, rash erythematous, rash pruritic)

Significant Adverse Events

The ICH E3 guidance recommends that marked laboratory abnormalities not meeting the definition of SAEs also be considered significant AEs. These laboratory abnormalities are described in Laboratory Findings in Section 7.4.4 under Laboratory Findings. In addition, the ICH E3 guidance considers other potentially important abnormalities, such as serious AEs as potentially significant. Overall, a slightly higher percentage of patients in Arm B (47%) experienced any Grade 3 or 4 TEAE than in Arm A (40%). The most frequent Grade 3 or 4 TEAEs seen overall in Trial ALTA were blood CPK increased (5.9%), hypertension (4.1%), lipase increased (3.2%), and rash (2.7%). Pneumonitis (2.3%), back pain (1.8%), and hypoxia (1.4%) were also present in more than ≥ 3 patients overall.

Laboratory Findings

Table 43 lists the percentage of patients with any worsening chemistry values from baseline to post-baseline by CTCAE grade shifts. The most common grade shifts from baseline to any worsening from baseline in both arms were AST increased (112 [51%] patients), glucose increased (95 [43%] patients), creatine phosphokinase (CPK) increased (82 [37%] patients), ALT increased (81 [37%] patients), amylase increased (72 [33%] patients), and lipase increased (72 [33%] patients). The most common grade shifts to post-baseline Grade 3-4 were CPK increased (16 [7%] patients) and lipase increased (11 [5%] patients).

Table 43: Shift in Chemistry Laboratory Parameters from Baseline in Trial ALTA (Reviewer Table)

Laboratory Parameter	Arm A 90 mg regimen N=109 n (%)		Arm B 180 mg regimen[1] N=110 n (%)	
	Shift to Any Grade	Shift to Grade 3-4	Shift to Any Grade	Shift to Grade 3-4
AST (SGOT) increased	41 (38)	1 (0.9)	71 (65)	0
Glucose increased	41 (38)	4 (3.7)	54 (49)	4 (3.6)
Creatine phosphokinase increased	29 (27)	3 (2.8)	53 (48)	13 (12)
ALT (SGPT) increased	37 (34)	0	44 (40)	3 (2.7)
Amylase increased	29 (27)	4 (3.7)	43 (39)	3 (2.7)
Lipase increased	23 (21)	5 (4.6)	49 (45)	6 (5.5)
Alkaline phosphatase increased	16 (15)	1 (0.9)	32 (29)	1 (0.9)
aPTT increased	24 (22)	2 (1.8)	22 (20)	1 (0.9)
Phosphorous decreased	16 (15)	2 (1.8)	25 (23)	4 (3.6)
Magnesium decreased	20 (18)	0	18 (16)	0
Sodium decreased	18 (17)	6 (5.5)	19 (17)	3 (2.7)
Calcium increased	11 (10)	0	16 (15)	0
Potassium decreased	9 (8)	1 (0.9)	19 (17)	1 (0.9)
Potassium increased	12 (11)	0	10 (9)	0

Laboratory Parameter	Arm A 90 mg regimen N=109 n (%)		Arm B 180 mg regimen[1] N=110 n (%)	
	Shift to Any Grade	Shift to Grade 3-4	Shift to Any Grade	Shift to Grade 3-4
Albumin decreased	4 (3.7)	1 (0.9)	8 (7)	0
Calcium decreased	4 (3.7)	0	6 (5.5)	0
INR increased	5 (4.6)	1 (0.9)	5 (4.5)	2 (1.8)
Magnesium increased	5 (4.6)	0	3 (2.7)	0
Sodium increased	4 (3.7)	0	4 (3.6)	0
Glucose decreased	2 (1.8)	0	3 (2.7)	0
Bilirubin increased	2 (1.8)	0	2 (1.8)	0

[1] The 180 mg regimen includes dosing at 90 mg daily for 7 days prior to escalation to 180 mg daily.

Table 44 shows the shifts from baseline to any post-baseline worsening that occurred in a greater proportion of patients in Arm B than in Arm A, either ≥10% absolute difference or ≥50% relative increase. There were no chemistry parameters that occurred in a greater proportion of patients in Arm A than Arm B.

Table 44: Shift in Chemistry Laboratory Parameters from Baseline to Any Post-baseline worsening in Trial ALTA (Reviewer Table)

Laboratory Parameter	Arm A 90 mg regimen N=109 n (%)	Arm B 180 mg regimen[1] N=110 n (%)
AST (SGOT) increased	41 (38)	71 (65)
Glucose increased[2]	41 (38)	54 (49)
Creatine phosphokinase increased	29 (27)	53 (48)
Amylase increased	29 (27)	43 (39)
Lipase increased	23 (21)	49 (45)
Alkaline phosphatase increased	16 (15)	32 (29)
aPTT increased	24 (22)	22 (20)
Potassium decreased	9 (8)	19 (17)

[1] The 180 mg regimen includes dosing at 90 mg daily for 7 days prior to escalation to 180 mg daily.
[2] Glucose levels were performed fasting.

The clinical chemistry parameter shift that occurred in a greater proportion (either ≥10% absolute difference or ≥50% relative increase) of patients from baseline Grade <3 to post-baseline Grade 3-4 in Arm A than in Arm B was sodium decreased (6 [5.5%] versus 3 [2.7%] patients). In Arm B, by the same definition, a greater proportion of patients had CPK increased (13 [12%] versus 3 [2.8%] patients), ALT increased (3 [2.8%] versus 0 patients), and phosphorous decreased (4 [3.6%] versus 2 [1.8%] patients).

Table 45 lists the percentage of patients with any worsening hematology laboratory values from baseline to post-baseline by CTCAE grade shifts.

Table 45: Shift in Hematology Laboratory Parameters from Baseline in Trial ALTA (Reviewer Table)

Laboratory Parameter	Arm A 90 mg regimen N=109 n (%)		Arm B 180 mg regimen[1] N=110 n (%)	
	Shift to Any Grade	Shift to Grade 3-4	Shift to Any Grade	Shift to Grade 3-4
Hemoglobin decreased	25 (23)	1 (0.9)	44 (40)	1 (0.9)
Lymphopenia	21 (19)	3 (2.8)	30 (27)	5 (4.5)
ANC decreased	7 (6)	3 (2.8)	15 (14)	1 (0.9)
Platelets decreased	7 (6)	0	6 (5.5)	0

[1] The 180 mg regimen includes dosing at 90 mg daily for 7 days prior to escalation to 180 mg daily.

Insulin was evaluated because there was preclinical evidence of brigatinib inhibition of the insulin-like growth factor receptor and may lead to insulin resistance and elevated blood glucose levels. Shifts to high range values from baseline were reported in 95 (43%) of patients overall (Arm A: 40 [37%] and Arm B: 55 [50%]). Table 46 shows the shift in insulin from baseline to highest or lowest post-baseline category.

Table 46: Shift in Insulin from Baseline to Highest or Lowest Post-baseline Range Category

Laboratory Parameter	Arm A 90 mg regimen N=109 n (%)	Arm B 180 mg regimen[1] N=110 n (%)
Insulin shift to lowest value[2]		
No change from baseline	77 (71)	79 (72)
Shift to Low	6 (5.5)	7 (6.4)
Normal to Low	6 (5.5)	4 (3.6)
High to Low	0	0
Unknown to Low	0	3 (2.7)
Insulin shift to highest value		
No change from baseline	58 (53)	43 (39)
Shift to High	40 (37)	55 (50)
Low to High	2 (1.8)	3 (2.7)
Normal to High	36 (33)	48 (44)
Unknown to High	2 (1.8)	4 (3.6)

[1] The 180 mg regimen includes dosing at 90 mg daily for 7 days prior to escalation to 180 mg daily.
[2] Insulin levels were performed fasting.

ISS laboratory shift analysis
Laboratory shift results in AP26113-11-101 were available for 14 patients at the 90 mg dose level and for 28 patients at the 180 mg dose level. Review of the Applicant's shift tables for the

ISS population does not identify any new laboratory safety signals, given the small number of patients from AP26113-11-101. Of note, no CPK CTCAE grade shifts were noted in that trial.

Ultimately, increased glucose and other laboratory abnormalities will be described in product labeling. Uncertainty exists in regards to the contribuation of brigatinib to some of these abnormalities (e.g., a non-fasting glucose level might have triggered an elevated level). Increased CPK levels and elevated pancreatic enzyme levels will be described in the Warnings Section of labeling to ensure monitoring.

Vital Signs

Bradycardia is considered a class effect of ALK inhibitors and the Applicant identified bradycaria as an event of special interest. The Applicant performed an analysis of bradycardic heart rate values with a heart rate of < 50 bpm and ≥ 25% reduction from baseline. Three (3) patients across both arms (1.4%) with ≥ 1 post-baseline ECG were noted meet these thresholds, 2 in Arm A and one in Arm B. A heart rate of < 60 bpm was noted in 33 (31%) of patients in Arm A and 42 (40%) of patients in Arm B. See Table 47 for heart rate shift from baseline by ECG.

Table 47: Heart Rate Shift from Baseline by ECG

	Arm A 90 mg regimen N=106 n (%)	**Arm B 180 mg regimen[1] N=105 n (%)**
Heart rate (bpm)		
< 60 bpm	33 (31)	42 (40)
< 50 bpm	6 (6)	8 (8)
Bradycardic (as defined above)	2 (1.9)	1 (1)
Tachycardic[2]	12 (11)	10 (10)

[1] The 180 mg regimen includes dosing at 90 mg daily for 7 days prior to escalation to 180 mg daily.
[2] Tachycardic is defined as heart rate >100 bpm and ≥25% increase from baseline.

Blood pressure shifts from baseline to worst post-baseline in Trial ALTA is presented in Table 48. Systolic blood pressure (SBP) shifts to 140-159 mmHg occurred in 22 (22%) patients in Trial ALTA and to ≥ 160 mmHg in 7 (7%) patients who had a normal (<120 mmHg) SBP at baseline. Diastolic blood pressure (DBP) shifts to post-baseline values of 80-89 mmHg, 90-99 mmHg, and ≥100 mmHg occurred in 65 (46%), 37 (26%), and 12 (9%) patients who had a normal (<80 mHg) DBP at baseline. Based on the Applicant's analysis of time to these changes from baseline in SBP and DBP occurred in similar proportions of patients in Arm A and Arm B.

Table 48: Blood Pressure Shifts from Baseline in Trial ALTA

	Arm A 90 mg regimen N=106 n (%)	**Arm B 180 mg regimen[1] N=105 n (%)**	**Total N=219 n (%)**
SBP at baseline <120	n=50	n=48	n=98

No change[2]	13 (26)	4 (8)	17 (17)
<120 to 120-139[2]	26 (52)	24 (50)	50 (51)
<120 to 140-159[2]	7 (14)	15 (31)	22 (22)
<120 to ≥160[2]	3 (6)	4 (8)	7 (7)
SBP shift from baseline			
One-level increase	57 (52)	54 (49)	111 (51)
Two-level increase	16 (15)	23 (21)	39 (18)
Three-level increase	3 (2.8)	4 (3.6)	7 (3.2)
DBP at baseline <80	n=68	n=72	n=140
No change[3]	14 (21)	9 (13)	23 (16)
<80 to 80-99[3]	30 (44)	35 (49)	65 (46)
<80 to 90-99[3]	16 (24)	27 (29)	37 (26)
<80 to ≥100[3]	6 (9)	6 (8)	12 (9)
DBP shift from baseline			
One-level increase	46 (42)	52 (47)	98 (45)
Two-level increase	23 (21)	26 (24)	49 (22)
Three-level increase	6 (5.5)	6 (5.5)	12 (5.5)

[1] The 180 mg regimen includes dosing at 90 mg daily for 7 days prior to escalation to 180 mg daily.
[2] Number of patients is expressed as a percentage of the subset of patients with SBP at baseline <120.
[3] Number of patients is expressed as a percentage of the subset of patients with DBP at baseline <80.

Bradycardia will be described in the Warnings section; as certain concomitant hypertension drugs could exacerbate bradycardia. Hypertension will also be included as a Warning in product labeling.

Electrocardiograms (ECGs)

See Section 7.4.4 Vitals for discussion of bradycardia.

QT

Increases from baseline QTcF of >60 ms occurred in 13/211 (6.2%) patients; 6 patients in Arm A and 7 patients in Arm B.

Although these results were observed, QT-IRT reviwed data based on Study AP26113-11-101 and concluded that no large changes (i.e., > 20 ms) in the QTcF interval were detected at the potential therapeutic doses 90 mg daily and 90 mg daily for 7 days followed by 180 mg daily. No significant positive relationship between brigatinib concentration and QTcF change from baseline was observed.

Furthermore, the clinical pharmacology review above stated that brigatinib inhibited hERG with IC50 >10 µM in vitro. The QT interval prolongation potential of brigatinib was assessed in 123 patients with advanced solid tumors following brigatinib 30 mg to 240 mg QD. The maximum

mean QTcF (corrected QT by the Fridericia method) change from baseline was <10 ms. An exposure-QT analysis suggested no concentration-dependent QTc interval prolongation.

Immunogenicity

This subsection is not relevant to this review, as brigatinib is not associated with a concern for immunogenicity.

7.4.5. Analysis of Submission-Specific Safety Issues

Early Onset Pulmonary Events
Interstitial lung disease (ILD)/pneumonitis is a recognized risk of TKIs in patients with NSCLC. Fatal events have occurred with crizotinib and ceritinib and one Grade 3 ILD was identified with alectinib. During early clinical development of brigatinib (AP26113-11-101), moderate and severe pulmonary adverse events (dyspnea, hypoxia, cough, pneumonia, pneumonitis, and radiographic findings of linear or ground glass opacities) were observed within 7 days following initiation of the drug, usually within the first 24-48 hours. Patients were managed with steroid treatment and supplemental oxygen which the Applicant states reversed the events, although some patients discontinued treatment after the events recurred with re-challenge. Because pulmonary events occurred more frequently with higher starting doses, the Applicant selected two doses for further study in Trial ALTA: 90 mg daily and 90 mg daily for 7 days followed by 180 mg daily.

Because the early onset of pulmonary symptoms has not been described with other ALK inhibitors, the Applicant sought to develop a prospective search strategy that differentiated between the early onset events and the later (> 7 days) pneumonitis-like events. The Applicant developed two case definitions: one for early onset pulmonary events (EOPE) and one for later-onset pneumonitis-like events. The case definitions were applied to pulmonary adverse events in both Trial ALTA and AP26113-11-101. The clinical safety reviewer reviewed the Applicant's prospective search strategy and preferred terms and determined it had selected an appropriate population from which the cases could be defined.

To be included in the case definition review for EOPE, two criteria were required:

- an adverse event coded to a MedDRA preferred term included in the prospective search strategy
- event onset within 14 days following initiation of brigatinib, dose-escalation of brigatinib, or re-initiation of brigatinib after a treatment interruption of at least 7 days

The Applicant reported that after a manual medical review of all SAEs, one case was not identified due to the pulmonary symptoms preceding the event of sudden death.

Any adverse event that occurred outside of the timeframe required to select potential EOPE cases was included in the case definition review for later onset pneumonitis-like events.

An EOPE event is defined as:

- Presence of a temporal relationship (defined as signs/symptoms beginning within the first 7 days following initiation, re-treatment after interruption, or dose escalation of brigatinib)
- Evidence of a pneumonitis-like process (e.g., hypoxia or dyspnea along with supportive imaging or pathology findings, such as ground glass opacities on computerized tomography (CT)/X-Ray, or diffuse alveolar damage on histopathology)
- Determination that an alternative etiology is unlikely (e.g., infectious, tumor, etc.)

Clear evidence of resolution of the event associated with dose interruption or recurrence of the event upon re-challenge was considered as supportive information.

Based on the above criteria, events were categorized as:

1) A Definite EOPE case (when criteria 1–3 above are all met)
2) A Possible EOPE case (when criteria 1 and 2 above are both met)
3) Not an EOPE case (when either criteria 1 or criteria 2 above are not met)

Similarly, the case definition for later onset pneumonitis-like event is the same as for EOPE except that the event occurs > 7 days following initiation, re-treatment after interruption, or dose escalation of brigatinib. The events were similarly categorized as for EOPE (e.g., definite, possible, and not a case) according to the same criteria. The definition of pneumonitis-like events included both EOPE and later onset pneumonitis-like events.

EOPE led to one possible death in Trial ALTA (pneumonia, described in Section 7.4.4 Deaths), and 14 (6.4%) patients overall had an EOPE event that was at least possibly related to brigatinib, all occurring at 90mg (i.e., prior to dose escalation if assigned to Arm B). EOPE led to dose discontinuations in 5 (2.3%) patients and drug interruption usually led to recovery. Seven of 14 (7/14) patients discontinued brigatinib permanently. In the other 7 patients, 6 had dose interruption of brigatinib and supportive care (antibiotics, steroids, supplemental oxygen, or a combination of these) with resolution of the pulmonary events. These patients were able to resume brigatinib. One patient continued brigatinib and the event resolved without dose modification.

Within Trial AP26113-11-101, 11/137 (8%) patients had at least a possible EOPE event with 10 of these cases at least Grade 3 and two possible deaths: one from hypoxia and one from pneumonia. In all but one of the 9 nonfatal cases, brigatinib was interrupted or withdrawn leading to resolution of the event. One patient with Grade 2 EOPE did not undergo dose reduction or treatment for the event, and the outcome was resolution. One event continued despite discontinuation of brigatinib.

The Applicant performed an analysis of Trial ALTA of the association of time between the last crizotinib dose (< 7 days versus ≥ 7 days and the first dose of brigatinib and determined that the relative risk of a < 7 day interval is 2.69 (95% CI 0.86, 8.32) with a chi-square p-value of 0.07.

The Applicant concluded that there appears to be a non-significant trend toward higher frequency of EOPEs with a shorter crizotinib washout.

The Applicant also performed an analysis of Trial ALTA of the additional risk of EOPE in elderly patients (age ≥ 65 years) and concluded that based on unadjusted multivariate analysis, age ≥ 65 was associated with higher EOPEs. Of note, the analysis is based on 7/167 (4.2%) patients aged < 65 years and 7/52 (13.5%) patients aged ≥ 65.

Hypertension
Hypertension is an event that is unique to brigatinib and not seen with other ALK-inhibitors. See Section 7.4.4 Vitals for an analysis of systolic and diastolic blood pressure shifts showing an increase in similar proportions between the two arms. An analysis performed by the Applicant shows that the mean SBP increase per year was 5.22 mmHg and the mean DBP increase per year was 5.17 mmHg.

Hypertension TEAEs (by SMQ) of any grade occurred in 35 (16%) of patients overall and in a greater proportion of patients in Arm B than in Arm A (21% [23] vs 11 [12%], respectively). Hypertension TEAE Grade ≥3 occurred in 5.6 (5.5%) of patients in Arm A and 7 (6.4%) of patients in Arm B. Hypertension led to brigatinib dose interruptions in 2 patients (1.8%) in Arm B and none in Arm A. One patient in Arm B had a dose reduction and there were no discontinuations due to a hypertension event. ARIAD included hypertension as a Warning in product labeling.

Bradycardia
Bradycardia is a class effect of ALK-inhibitor TKIs. Based on review of patients with at least one post-baseline ECG, 6 of 106 patients in Arm A (5.7%) and 8 of 105 patients in Arm B (7.6%) with at least one post-baseline ECG had bradycardia defined as less than 50 beats per minute.

Bradycardia TEAE was reported in 10 (4.6%) of patients overall, and was symptomatic in one patient (Grade 2). No Grade 3 or greater bradycardia was reported. There were no brigatinib dose interruptions, dose reductions, or dose discontinuations due to bradycardia events. ARIAD included bradycardia as a Warning in product labeling.

Gastrointestinal Events
The Applicant defined a composite term intended to capture abdominal pain, diarrhea, nausea/vomiting, constipation, and other GI disorders. The definition appears reasonable to the safety reviewer.

GI TEAEs occurred in 149/219 (68%) of patients overall (64% in Arm A and 79% in Arm B). The most common GI TEAEs were nausea (37%), diarrhea (29%), and vomiting (23%). Diarrhea appeared to be dose-related with 38% of patients in Arm B affected versus 19% of patients in Arm A. Grade ≥3 GI TEAEs occurred in 2.3% of patients overall. Gastrointestinal events of vomiting led to a dose interruption in 2.7% of patients, and nausea led to brigatinib dose

interruption in 0.9% of patients. Constipation, diarrhea, and dyspepsia led to brigatinib dose interruption in 1 patient each. Brigatinib dose reductions due to TEAEs of nausea and dyspepsia were reported in 2 (1.8%) patients and 1 (0.9%) patient, respectively in Arm B. No dose reductions for nausea or dyspepsia took place in Arm A. No patient discontinued brigatinib due to a GI event.

Pancreatic Events
In Trial ALTA, amylase elevations occurred in 27% of patients in the 90 mg regimen and 39% of patients in the 180 mg regimen. Lipase evaluations occurred in 21% of patients in the 90 mg regimen and 45% of patients in the 180 mg regimen. Grade 3-4 pancreatic enzyme elevation took place in 3.7% of patients in the 90 mg regimen and 2.7% of patients in the 180 mg regimen. There were no clinical pancreatitis AEs in Trial ALTA.

The Applicant used a prospective search strategy for both chemical and clinical pancreatic events. By this definition, pancreatic events of increased lipase and increased amylase led to a brigatinib dose interruption in 7 [3.2%] and 3 (1.4%) patients respectively. Increased lipase led to brigatinib dose reduction in 2 (0.9%) patients (one in each arm) and increased amylase in 1 (0.5%) patient. No patients discontinued brigatinib due to a pancreatic event.

In AP26113-11-101, there were two reported SAEs of Grade 3 pancreatitis, one in a patient who died from fungal sepsis in the setting of a Grade 3 pneumonitis (patient's dose was 240 mg daily), and the other who experienced the event approximately 3 weeks after discontinuation for progression with peritoneal carcinomatosis and obstructed hepatic ducts that resolved with stenting (patient's dose was 180 mg daily).

Elevated Insulin/Hyperglycemia events
A prospective search by the Applicant showed elevated insulin/hyperglycemia events of any grade in 12 (5.5%) patients overall. More events took place in Arm B (10 [9%] patients) than Arm A (2 [1.8%] patients). No TEAEs for diabetes mellitus were described in Arm A, and a Grade ≥ 3 event occurred in one patient in Arm B who did not have a pre-existing diagnosis of diabetes.

Hyperglycemia events led to dose interruption in one patient and there were no events of elevated insulin leading to an interruption. No dose reduction or discontinuation due to elevated insulin/hyperglycemia events.

Hepatic Events
Hepatic events have been described with several ALK-inhibitor TKIs. A prospective search by the Applicant showed hepatic events of any grade in 37 (17%) patients overall, and in a similar proportion in patients in Arm A and Arm B (17 [16%] and 20 [18%], respectively). The most common hepatic event was aspartate aminotransferase increased in 25 [11%] patients overall), which occurred in a greater proportion of patients in Arm B than in Arm A (14.5% versus 8.3%, respectively).

No clinically symptomatic hepatotoxicity events were reported and no patient met the laboratory criteria for a possible Hy's Law case. No patients had TEAE Grade ≥3 associated with hepatic laboratory values. There were no hepatic events that led to brigatinib dose interruption, dose reduction, or dose discontinuation.

Skin and Subcutaneous Tissue SOC Events
The most common skin event in patients overall was rash (26 [12%]), which occurred in a greater proportion of patients in Arm B (18 [16%]) than in Arm A (8 [7%]). Skin events of Grade ≥3 occurred in 7 (3.2%) of patients overall, with rash being the most common (4 [1.8%]). The skin events of rash led to dose interruption in 5 (2.3%) patients overall.

The skin events of rash led to dose reduction in 2 (0.9%) patients overall. A skin event led to brigatinib discontinuation in one patient with a history of drug-induced dermatitis who developed angioedema. Rash is described in product labeling.

Vision disorder events
Vision disorders have been reported in other ALK-inhibitor TKIs. The Applicant used a prospective strategy to identify affected patients which appeared reasonable to the clinical reviewer. Vision disorder events of any grade occurred in 9 (8%) patients in Arm A and 16 (15%) patients in Arm B. The most common preferred term was vision blurred which occurred in a similar proportion of patients in both arms (3 [2.8%] patients overall). The applicant included Visual disturbance as a Warning in product labeling.

There was a single Grade 3 event of macular edema that resolved with interruption of 1 month. Brigatinib was restarted at a lower dose, and Grade 2 macular edema was reported and did not abate with interruption.

7.4.6. Safety Analyses by Demographic Subgroups

Age
In Trial ALTA, 22/109 (20%) patients who received the 90 mg regimen and 30/110 (27%) who received the 180 mg regimen were ≥ 65 years of age. Table 49 shows the incidences of TEAEs by age and treatment group. There were slightly more Grade 3-4 AEs in those ≥65 years at the 90 mg dose level, but at the 180 mg dose level, the incidence of and Grade 3-4 AEs in patients ≥65 years was generally consistent with the incidence rate of AEs experienced in patients <65 years. In general, a substantive review of safety by age could not be conducted based on the limited number of patients 65 years of age or older. The Applicant conducted a multivariate analysis and concluded that increased age was associated with an increased risk of early onset pulmonary adverse reactions.

Table 49: Comparison of Treatment-Emergent Adverse Events by Age in Trial ALTA (Reviewer Table)

	Arm A 90 mg regimen N=109 n (%)		Arm B 180 mg regimen[1] N=110 n (%)	
	< 65 N=84[2] n (%)	≥ 65 N=22 n (%)	< 65 N=80 n (%)	≥ 65 N=30 n (%)
Any TEAE	84 (97)	22 (100)	80 (100)	30 (100)
Grade 3-4 TEAEs	26 (31)	12 (55)	37 (46)	15 (50)
Grade 5 TEAEs	14 (17)	4 (18)	7 (9)	2 (7)
Any SAE	33 (39)	8 (36)	31 (39)	13 (43)
TEAEs leading to discontinuation	5 (6)	2	7 (9)	4 (13)

[1] The 180 mg regimen includes dosing at 90 mg daily for 7 days prior to escalation to 180 mg daily.
[2] No AEs were reported in 3 patients < 65 years of age in Arm A.

Gender
In Trial ALTA, female patients represented of 59/109 (54%) patients who received the 90 mg regimen and 64/110 (58%) who received the 180 mg regimen. Table 50 shows the incidence of TEAEs by gender and treatment group. Overall there is no consistent pattern of TEAE differences between genders and no evidence that gender affects tolerability of brigatinib.

Table 50: Comparison of Treatment-Emergent Adverse Events by Gender in Trial ALTA (Reviewer Table)

	Arm A 90 mg regimen N=109 n (%)		Arm B 180 mg regimen[1] N=110 n (%)	
	Male N=47[2]	Female N=59	Male N=46	Female N=64
Any TEAE	47 (94)	59 (100)	(100)	(100)
Grade 3-4 TEAEs	19 (40)	19 (32)	19 (41)	33 (52)
Grade 5 TEAEs	9 (19)	9 (15)	5 (11)	4 (6)
Any SAE	19 (40)	22(37)	21 (46)	23 (36)
TEAEs leading to discontinuation	4 (8.5)	3 (5.1)	7 (15)	4 (6)

[1] The 180 mg regimen includes dosing at 90 mg daily for 7 days prior to escalation to 180 mg daily.
[2] No TEAEs were reported in 3 male patients in Arm A.

Race
In the safety population of Trial ALTA, the majority of patients in both arms where White. Table 51 shows the incidence of TEAEs by race and treatment group. Across all TEAEs, Grade 3-4 TEAEs, SAEs, and TEAEs leading to discontinuation, Asian patients appeared to tolerate brigatinib better than White patients. Nevertheless, the limited number of patients precludes any definitive statements regarding safety across different racial/ethnic groups.

Table 51: Comparison of Treatment-Emergent Adverse Events by Race in Trial ALTA (Reviewer Table)[1]

	Arm A 90 mg regimen N=109 n (%)		Arm B 180 mg regimen[2] N=110 n (%)	
	White N=70[3]	Asian N=39[3]	White N=76	Asian N=30
Any TEAE	68 (97)	38 (97)	76 (100)	30 (100)
Grade 3-4 TEAEs	29 (41)	9 (23)	35 (46)	14 (18)
Grade 5 TEAEs	14 (20)	4 (10)	9 (12)	0
Any SAE	28 (40)	13 (33)	32 (42)	11 (14)
TEAEs leading to discontinuation	4 (6)	3 (8)	9 (12)	3 (3.9)

[1] There were 3 Black patients enrolled overall in Trial ALTA. Additionally, there were 2 patients of unknown race in Arm B. No meaningful analysis could be performed given the small number so these patients were excluded from the table.
[2] The 180 mg regimen includes dosing at 90 mg daily for 7 days prior to escalation to 180 mg daily.
[3] No TEAEs were reported in 2 White patients and one Asian patient.

7.4.7. Specific Safety Studies/Clinical Trials

There were no additional studies performed to evaluate any specific safety concerns.

7.4.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No clinical studies have been performed to assess the potential of brigatinib for carcinogenicity. One SAE (Grade 3) of metastatic melanoma was diagnosed in a patient in AP26113-11-101 at the 180 mg dose level who had a prior history of left shoulder melanoma. The diagnosis was made on Day 20 of treatment. The investigator assessed that the event was not related to brigatinib and this reviewer agrees with the assessment.

Pediatrics and Assessment of Effects on Growth

The safety and effectiveness of brigatinib in pediatric patients has not been established.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no cases of brigatinib overdose in either clinical trial. There are no concerns regarding the potential for abuse, withdrawal, or rebound with brigatinib. On the basis of its pharmacological properties, the risk of abuse or misuse of brigatinib is low.

7.4.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

There is no postmarketing experience of brigatinib.

Expectations on Safety in the Postmarket Setting

There are no recommended postmarking requirements for safety-related concerns with brigatinib at this time. Safety data from the ongoing confirmatory trial will be analyzed for new safety signals not presented in the label and any changes required in regards to known safety issues. Postmarketing safety will be assessed through routine pharmacovigilance.

7.4.10. Integrated Assessment of Safety

Integrated Assessment of Safety
The safety of brigatinib in patients with ALK-positive NSCLC whose disease has progressed on crizotinib was primarily based on the 219 patients who received at least one dose of brigatinib in Trial ALTA, an open-label, randomized, non-comparative trial of two different doses of brigatinib. While the toxicities observed were reasonable for the indicated dose of 90 mg daily for 7 days followed by 180 mg daily until progression (the 180 mg regimen), the 90 mg daily regimen also appeared to have activity with a somewhat lower side-effect profile.

Of particular concern were the early-onset pulmonary events (EOPE) which appeared to occur with brigatinib in a much earlier timeframe (7 days with median time to onset of 2 days) than interstitial lung disease/pneumonitis seen with other ALK inhibitors. Furthermore, there is some evidence that events may occur if the interval between crizotinib and brigatinib is <7 days, and that elderly (age ≥65 years) patients may be at higher risk of these pulmonary events. This unique toxicity led to the decision to initiate dosing at 90 mg daily for 7 days prior to escalation to 180 mg daily as a means to reduce the frequency of events. EOPE led to one possible death in Trial ALTA, and 14 (6.4%) patients overall had an EOPE event, all occurring at 90 mg (i.e., prior to dose escalation if assigned to Arm B). EOPE led to permanent dose discontinuations in 7 (3%) of patients. Drug interruption and supportive care usually led to recovery and management guidelines should be included in the Warnings and Precautions of the USPI according to management in Trial ALTA.

Other safety issues identified with brigatinib, including class effects, that should be included in the Warnings and Precautions section of the USPI include hypertension (also a unique toxicity to this particular ALK-inhibitor), late-onset pneumonitis events, bradycardia, vision disturbances, CPK elevation, and pancreatic enzyme elevation.

The clinical review of safety for this NDA determined that the safety profile of brigatinib is acceptable in patients with ALK-positive NSCLC whose disease has progressed on crizotinib and especially in those patients with brain metastases given the intracranial responses. The most serious risk of brigatinib is the early onset pulmonary toxicity. Recommendation for safe and effective use of brigatinib, including monitoring and management guidelines, will be addressed in labeling.

SUMMARY AND CONCLUSIONS

7.5. Statistical Issues

There were no major statistical issues that impacted the overall conclusions of Trial ALTA.

7.6. Conclusions and Recommendations

NSCLC has an extremely poor prognosis overall, and ALK-positive patients who have progressed on crizotinib have limited options for treatment. Furthermore, there is an unmet medical need for this population based on the high rate of intracranial metastases and limited response at this site to other ALK-inhibitors.

Based on the data from the 222 enrolled patients in Study AP26113-13-201, the IRC-confirmed percentage of responders were 48.2% (95% CI: 38.7, 57.9) for subjects in Arm A and 52.7% (95% CI: 43, 62.3) for subjects in Arm B. The investigator-confirmed percentage of responders were 44.6% (95% CI: 35.2, 54.3) for subjects in Arm A and 53.6% (95% CI: 43.9, 63.2) for subjects in Arm B.

As of the data-cutoff date of May 31, 2016, the IRC-confirmed median DoR was 13.8 months for both Arms A and B. The lower bounds for the 95% confidence interval were 7.4 and 9.3 months for Arms A and B, respectively. The upper bounds for the 95% confidence intervals were not estimable in both arms.

As of the data-cutoff date of February 29, 2016, the investigator-confirmed median DoR was 13.8 months (95% CI: 5.6, 13.8) and 11.1 months (95% CI: 9.2, 13.8) for Arms A and B, respectively. The lower bounds for the 95% confidence interval were 5.6 and 9.2 months for Arms A and B, respectively. The upper bound for the 95% confidence intervals was 13.8 months for both arms A and B.

Despite the lack of a control arm in Trial ALTA, a clinically meaningful improvement in ORR and DoR was observed as compared to historical control. Furthermore, intracranial response rate appeared promising.

Accelerated approval is recommended for brigatinib at the dose of 90 mg daily for 7 days followed by 180 mg daily until disease progression or unacceptable toxicity. Accelerated approval is recommended given the uncertainty regarding the treatment effects observed in ALTA and the ultimate clinical benefit of brigatinib. ARIAD is conducting an ongoing randomized study assessing the effects of brigatinib versus crizotinib in order to confirm the clinical benefit.

X	X
Thomas Ly, Ph.D. Primary Statistical Reviewer	Kun He, Ph.D. Statistical Team Leader
X	X
M. Naomi Horiba, M.D., M.P.H. Primary Clinical Reviewer	Steven Lemery, M.D., M.H.S. Clinical Team Leader

8 Advisory Committee Meeting and Other External Consultations

The Division did not obtain the advice of the Oncologic Drug Advisory Committee (ODAC) for this NDA. The Division obtained the advice of a practicing oncologist with expertise in lung cancer and a patient (physician) with a history of lung cancer. Both Special Government Employees provided agreement in regards to the favorable risk-benefit assessment in the indicated patient population with unmed need.

9 Pediatrics

Trials with safety or efficacy data pertaining to pediatric patients were not submitted. The NDA is exempt from the requirement to assess safety and effectiveness of the product for the claimed indication in all pediatric age categories under 21 CFR 314.55(d), Exemption for Orphan Drugs.

10 Labeling Recommendations

10.1. Prescribing Information

In general, DOP2 revised labeling for brevity and clarity. Some information was moved to different sections of labeling (e.g., clin-pharm and toxicology). Such changes are not described below. The remainder of this section of the review will only focus on high-level issues regarding the amended label submitted by ARIAD.

Section 1: For the indication, DOP2 agreed with inclusion of patients refractory to crizotinib. Although no patients in trial ALTA were intolerant to crizotinib, 2 patients in AP26113-11-101 had previously discontinued crizotinib for toxicity and subsequently tolerated treatment with brigatinib.

Section 5: DOP2 recommended including a Warning regarding hyperglycemia because glucose levels can be monitored and close monitoring may mitigate severe toxicity if glucose levels are controlled (or brigatinib is dose reduced).

Section 2.3: OCP recommend inclusion of this section describing dose modifications of brigatinib for patients who cannot avoid a strong CYP3A inhibitor.

Section 7.1: OCP recommended deletion of the section regarding (b) (4) .

Section 7.2: OCP recommended deletion of a statement that use (b) (4) as available data did not appear to support this statement.

Section (b) (4)

Section 14: DOP2 recommended deletion of (b) (4) .

10.2. Patient Labeling

ARIAD proposed patient labeling. The proposed patient labeling included Warnings described in the package insert.

11 Risk Evaluation and Mitigation Strategies (REMS)

There are no additional risk management strategies required beyond the recommended labeling. Although brigatinib can cause severe/serious toxicities, it will be prescribed by oncologists who by training understand how to monitor and manage such toxicities. Oncologists, by training, also obtain informed consent prior to prescribing drugs that can cause severe toxicities. Subsequent subsections are not applicable for this review and have been omitted.

12 Postmarketing Requirements and Commitments

This application is being approved under accelerated approval regulations 21 CFR 314.510 and therefore contains one requirement to confirm clinical benefit. There are three trials to assess specific safety concerns required under FDAAA 505(o) regulations. In addition there are three agreed upon commitments that will provide additional useful characterization of clinical responses and pharmacokinetic interaction data. The postmarketing requirements and commitments are as follows:

Accelerated Approval Requirement under 21 CFR 314.510 Subpart H

PMR 3190-1: Conduct and submit the results of at least one multicenter, randomized clinical trial that verifies and describes the clinical benefit of brigatinib in patients with metastatic anaplastic lymphoma kinase positive non-small cell lung cancer (NSCLC).

Safety Requirements under FDAAA 505(o)

PMR 3190-2: Conduct a physiologically-based pharmacokinetic modeling study to evaluate the effect of repeat doses of a moderate CYP3A4 inhibitor on the single dose pharmacokinetics of brigatinib to address the potential for excessive drug toxicity.

PMR 3190-3: Complete a clinical pharmacokinetic trial to determine an appropriate dose of brigatinib to minimize toxicity in patients with renal impairment.

PMR 3190-4: Complete a clinical pharmacokinetic trial to determine an appropriate dose of brigatinib to minimize toxicity in patients with hepatic impairment.

Postmarketing commitments under 505B regulations

PMC 3190-5: Submit the final analysis of intracranial response duration based upon independent radiology reviewer assessment of imaging data collected for two years following the date of enrollment of the last patient in Study AP26113-13-201.

PMC 3190-6: Conduct a physiologically-based pharmacokinetic modeling study to evaluate the effect of repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of brigatinib to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations.

PMC 3190-7: Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of brigatinib on the single dose pharmacokinetics of midazolam (a sensitive CYP3A4 substrate) to assess the magnitude of decreased exposures of a sensitive CYP3A4 substrate and to determine appropriate dosing recommendations.

13 Appendices

13.1. References

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13.2. Financial Disclosure

Signed financial disclosure was obtained by the Applicant for all but two sub-investigators for Trial AP26113-11-101 and all but one sub-investigator for Trial ALTA. Both sub-investigators in Trial AP26113-11-101 were from the same site and the Applicant attempted to obtain disclosure on 5 occasions. The two investigators are reportedly no longer working at that site. For the sub-investigator on Trial ALTA, the Applicant tried to obtain disclosure on at least 5 occasions. The Applicant acted with due diligence to obtain the financial disclosure for these sub-investigators. Due to the small numbers of patients enrolled at these sites, the lack of financial disclosure is not expected to affect the integrity of the data.

One sub-investigator for Trial AP26113-11-101 at (b) (6) where (b) (6) patients were enrolled disclosed an equity interest in the Applicant as defined in 21 CFR 54.2(b). The sub-investigator is not listed as an investigator in Trial ALTA from which primary safety and efficacy data were obtained.

Covered Clinical Study (Name and/or Number): AP26113-11-101

Was a list of clinical investigators provided: Yes	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 164		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor: 1 Sponsor of covered study: _____		
Is an attachment provided with details	Yes ☒	No ☐ (Request details from

of the disclosable financial interests/arrangements:		Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 2		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): Trial ALTA

Was a list of clinical investigators provided: Yes	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 546		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3. Nonclinical Pharmacology/Toxicology

Additional Histopathological findings from Study (b) (4)-69505 (6-month rat study)

Histopathological Findings in Rat 25 mg/kg/day Early Primary Necropsy (Week 7) and Early Recovery Necropsy (Week 15) Animals

Sex	Males		Females	
Number of Animals	15	6	15	8
Findings Time Point (weeks)	7	15	7	15
Epididymides, cellular debris, minimal	4	1		
mild	6	4		
moderate	1	-		
Reduced sperm, luminal, minimal	5	-		
mild	4	2		
moderate	4	2		
severe	0	1		
Heart, degeneration, myocardial, minimal	4	-	1	-
mild	2	-	-	-
moderate	-	-	1	-
Kidneys, dilation, tubular, minimal	7	1	4	3
mild	4	-	7	-
moderate	1	-	3	0
LN, Axillary, reduced cellularity, minimal	4	1	2	1
mild	7	3	11	5
moderate	2	0	1	1
Pancreas, islet fibroplasia, minimal	3	-	4	1
mild	6	2	3	-
moderate	3	-	2	-
severe	2	-	-	-
Atrophy, acinar, minimal	2	-	2	4
moderate	1	-	-	-
Spleen, reduced cellularity, minimal	5	-	6	-
mild	8	-	7	-
moderate	1	-	1	-
Pigment, brown, minimal	6	-	1	-
mild	8	-	10	3
moderate	-	-	3	-
Testes, degeneration, tubular, minimal	5	1		
mild	1	1		
moderate	1	1		
severe	1	3		
Thymus, reduced cellularity, minimal	1	3	4	-
mild	3	-	5	1
moderate	2	-	1	1

Histopathological Findings Week 34 Rat Recovery Necropsy, Groups 1-3

Sex	Males			Females		
Group	1	2	3	1	2	3
Number of Animals Examined	9	10	8	10	9	8
Findings Dosage (mg/kg/day)	0	7.5	15	0	7.5	15
Adrenal cortex, angiectasis, mild,	-	-	1			
thrombosis, moderate				-	-	1
Epididymides, reduced sperm, luminal, minimal	-	-	1			
mild	-	-	1			
severe	1	-	-			
Eyes, hemorrhage, acute, moderate				-	-	1
Phthisis, bulbi, present				-	-	1
Pigment, brown, mild				-	-	1
Kidney, nephropathy, chronic progressive, minimal				2	4	3
mild				-	1	2
moderate	1	-	4	-	-	1
Lung, hemorrhage, acute, moderate				-	-	1
Pancreas, atrophy, acinar, minimal	1	1	2	-	2	2
mild	1	1	2	-	-	1
moderate	-	1	1			
Testes, degeneration, tubular, minimal	-	3	3			
moderate		1	2			
severe	1	-	-			
Thymus, hemorrhage, acute, minimal	3	1	2			
mild	1	1	2	1	-	1
moderate				-	-	1
Uterus, dilation, luminal, moderate				-	-	1
Vagina, estrous cycle, proestrus present				-	2	1

13.4. OCP Appendices (Technical documents supporting OCP recommendations)

Office of Clinical Pharmacology: Pharmacometrics Review

1 Summary of Findings

In pivotal trial Study 201, two once daily (QD) dosing regimens (Arm A: 90 mg QD, continuously; Arm B: 180 mg QD with a first 7-day lead-in at 90 mg QD) were tested. The primary objective was to determine the objective response rate (ORR). Secondary objectives included the evaluation of PFS, OS, treatment duration, CNS response and PFS, safety, tolerability, population pharmacokinetics (PopPK), exposure-efficacy relationship, exposure-safety relationship, etc.

Exploratory dose-response analyses suggested the following:

- The investigator–assessed confirmed ORR was 44.6% (50/112) for patients in Arm A (97.5% CI: 34.0, 55.6) and 53.6% (59/110) for patients in Arm B (97.5% CI: 42.6, 64.5).
- The IRC assessed confirmed ORR was 48.2 (54/112) for Arm A (95%CI: 38.7-57.9), and 52.7 (58/110) for Arm B (95% CI: 43.0-62.3).
- Arm B resulted in a higher intracranial response rate in patients with brain metastases.
- Arm B showed an increase in median progression-free survival (15.6 months in Arm B versus 9.2 months in Arm A).
- Patients in Arm B had a higher rate of 1-year overall survival (79.5% versus 70.6%).
- Patients in Arm B had fewer discontinuations and fewer deaths due to disease progression.

Although there was a dose-efficacy relationship, the exposure-efficacy relationship (ER) was relatively flat between the two arms based on the geometric mean of the steady-state trough concentrations. Considering the >30% dose interruption and dose reduction in the both arms, we conducted exploratory sensitivity survival analysis using simulated varying daily exposure as a covariate. This analysis demonstrated a positive ER relationship for PFS and OS, which is consistent with the reported dose-response relationship (DR). The ER relationship for safety from our analysis based on the predicted mean daily AUC of the second week is also consistent with DR. The overall safety profile and low incidence of dose modification (20%) observed in Arm B support the use of the proposed higher dose (90/180 mg) with dose modification in the event of adverse reactions.

The proposed dose reduction strategy in the event of adverse reactions to the lowest acceptable dose of 60 mg QD is reasonable as the minimally effective brigatinib dose resulting in mean steady-state trough concentrations that exceed the IC_{50} for inhibition of EML4-ALK and 17 ALK secondary mutations associated with clinical resistance to crizotinib is 60 mg. Following 60 mg QD, the steady-state maximum concentrations exceed the IC_{90} for inhibition of EML4-ALK and 17 ALK secondary mutations associated with clinical resistance to crizotinib.

2 Key Review Questions

The purpose of this review is to address the following key questions.

2.1.1 Do dose/exposure relationships for efficacy and safety support the proposed dosing regimen: 90 mg QD for 7 days followed by 180 mg QD administered orally?

Based on dose/exposure-response analysis, the proposed dosing regimen of 180 mg QD is acceptable.

Reference ID: 4090771

For efficacy:

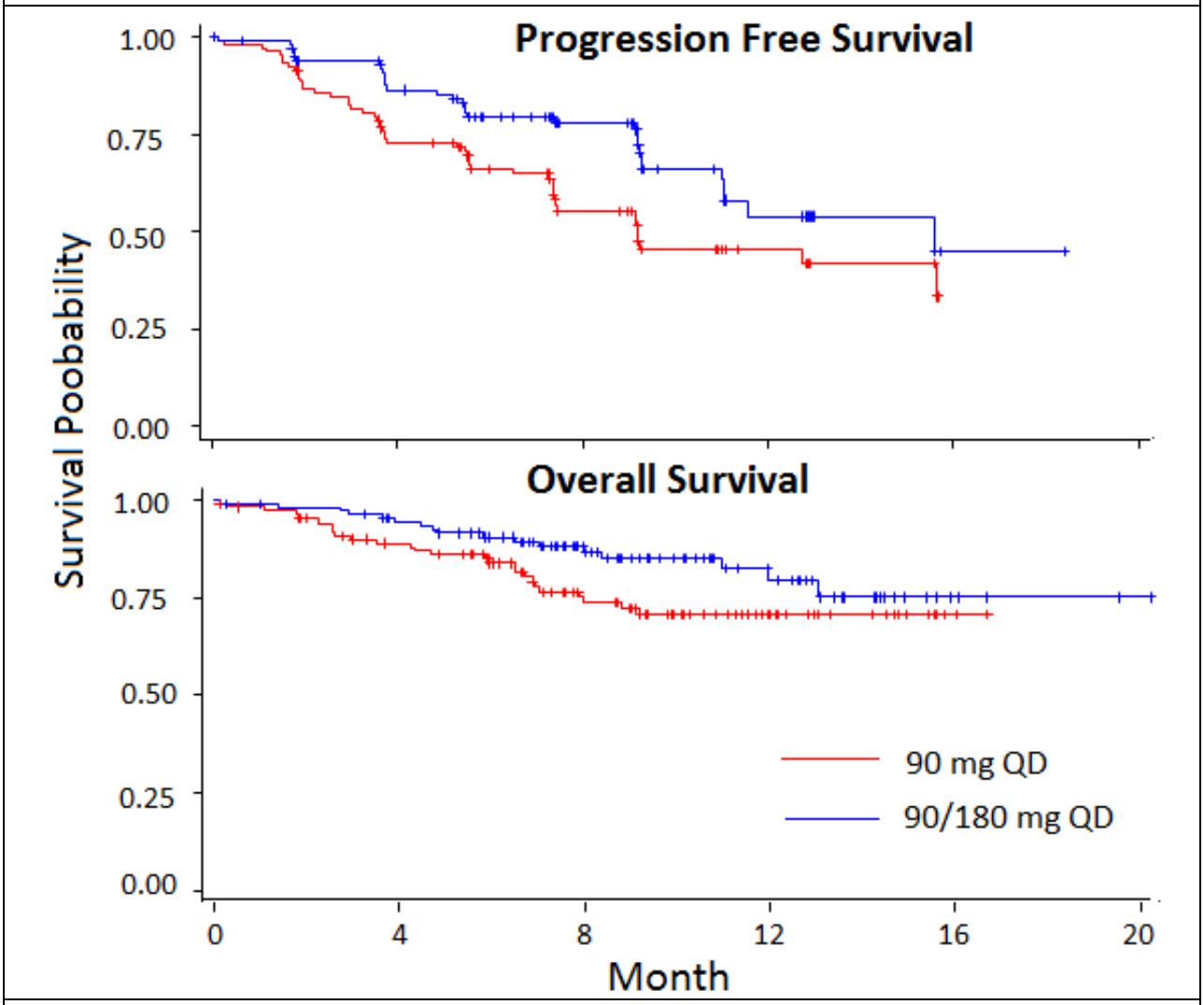
In Study 201, the Phase II pivotal trial, 222 NSCLC patients were randomized 1:1 to either Arm A (brigatinib 90 mg daily) or Arm B (brigatinib 90 mg QD for first 7 days and 180 mg QD afterwards). Arm B appeared to be numerically more efficacious than Arm A. The major clinical efficacy results by arm are presented in Table 52 for objective response rate (ORR) and in Figure 8 for progression free survival (PFS) and overall survival (OS).

Table 52: Summary of IRC Assessed Objective Responses: ALK+ NSCLC Patients Previously Treated with Crizotinib in Study 201

	Arm A, 90 mg QD N=112	Arm B, 90 mg QD → 180 mg QD N=110
Objective Response Rate		
Confirmed Objective Response, n(%, 95CI)	54 (48.2, 38.7-57.9)	58 (52.7, 43.0-62.3)
Disease Control Rate, n(%, 95CI)	87 (77.7, 68.8-85.0)	92 (83.6, 75.4-90.0)
Best Overall Response, n (%)		
Confirmed CR	4 (3.6)	5 (4.5)
Confirmed PR	50 (44.6)	53 (48.2)
Single PR	1 (0.9)	0
Stable Disease	32 (28.6)	34 (30.9)
Progressive Disease	14 (12.5)	5 (4.5)
Not Evaluable	11 (9.8)	13 (11.8)
Patients with Measurable Brain Metastases		
Confirmed Intracranial ORR, n(%, 95CI)	11 (42.3, 23.4-63.1)	12 (66.7, 41.0-86.7)
Intracranial Disease Control Rate, n(%, 95CI)	22 (84.6, 65.1-95.6)	15 (83.3, 58.6-96.4)

Source: Table 5 in Page 34 and Table 7 in Page 38 of Clinical Overview.

Figure 8: IRC-Assessed Systemic Progression-Free Survival and Overall Survival (ITT Population: by Treatment Group)



Source: Figure 11-6 in Page 92 and Figure 11-11 in Page 103 of Applicant's clinical study report for Study 201.

Exploratory analysis of dose-response and the exposure-response for ORR also suggests additional efficacy for the high dose arm (Table 53). Considering the >30% dose interruption and dose reduction in the both arms, we also conducted exploratory sensitivity survival analysis using simulated varying daily exposure as a covariate. This analysis demonstrated a positive ER relationship for PFS and OS, which is consistent with the reported dose-response relationship (DR).

Table 53: Dose-Efficacy and Exploratory Exposure-Efficacy Relationship of Study 201			
Arm B (90/180) vs Arm A (90)	ORR Odds Ratio (95CI)	PFS Hazard Ratio (95CI)	OS Hazard Ratio (95CI)
Univariate Dose-Efficacy Analysis	1.24 (0.73,2.11)	0.55 (0.35,0.86)	0.57 (0.31,1.05)
Multivariate Dose-Efficacy Analysis[a]	1.11 (0.63,1.95)	0.76 (0.47,1.23)	0.86 (0.44,1.66)
Exposure-Efficacy Analysis[b]	1.11 (0.89,1.38)	0.98 (0.84,1.14)	0.97 (0.78,1.21)

[a] Binominal logistic regression for ORR and COXPH regression for PFS and OS using model: Y~Arm + REGION + DIAGBRN + PCBRESPN + ECOGBLN + NUMSITES + BASEDIAM + RACE.
[b] Binominal logistic regression for ORR and COXPH regression for PFS and OS using model: Y~ $AUC_{2responseDate}$ + REGION + DIAGBRN + PCBRESPN + ECOGBLN + NUMSITES + BASEDIAM + RACE, $AUC_{2responseDate}$.
Note: DIAGBRN: brain metastases at study entry with values 1 or 0; PCBRESPN: best response to prior crizotinib regimen with value 1 for complete response and partial response and 0 for otherwise; ECOGBLN: baseline ECOG performance status with values of 0, 1 or 2; NUMSITES: number of metastatic sites at study entry with values of 1 to 9; BASEDIAM: sum of diameters (in mm) of target lesions at baseline; $AUC_{2responseDate}$: mean daily AUC to response date of OR, PFS and OS, refer to Section 4.4.2 for the calculation.
Source: FDA reviewer's exploratory analysis based on applicant's datasets.

For safety:

The overall safety difference of the two arms is summarized in Table 54, where Arm B showed higher AE rates than Arm A in all items. Dose-response trend appeared for some treatment-related Grade3+ adverse events, such as blood creatinine phosphokinase increased, skin and subcutaneous tissue disorders, rash, pneumonitis, and pneumonia.

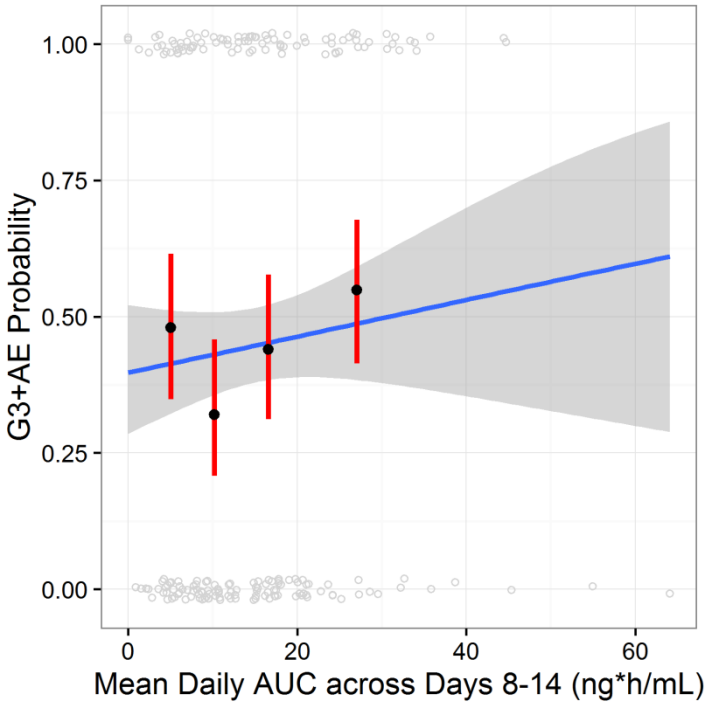
Table 54: Summary of Safety Endpoints in Study 201 that Showed Dose-Response Relationship		
	Arm A, 90 mg QD N=109	**Arm B, 90 mg QD → 180 mg QD, N=110**
Drug Exposure		
Dose Interruption of ≥3 days, n (%)	20 (18.3)	40 (36.4)
Dose Interruption due to AE, n (%)	35 (32.1)	50 (45.5)
Duration of Longest Dose Interruption ≥3 days, Mean ± SD (n), Min, Median, Max	8.8±3.43 (20), 4, 7.5, 16	12.9±10.15 (40), 3, 9.5, 57
Any Treatment Emergent AE		
Any treatment-related SAE, n (%)	8 (7.3)	18 (16.4)
Any treatment-related TEAE Grade ≥3	21 (19.3)	34 (30.9)
Any treatment-related SAE Grade ≥3, n (%)	6 (5.5)	10 (9.1)
Any TEAE leading to dose interruption, dose reduction, or brigatinib discontinuation, n (%)	36 (33.0)	55 (50.0)

Any TEAE leading to brigatinib discontinuation (primary reason), n (%)	3 (2.8)	9 (8.2)
Patients with ≥1 Treatment Related AE		
Diarrhea, n (%)	15 (13.8)	31 (28.2)
Blood creatinine phosphokinase increased, n (%)	9 (8.3)	31 (28.2)
Amylase increased, n (%)	8 (7.3)	15 (13.6)
Treatment-Related Grade ≥3 AE		
Blood Creatinine Phosphokinase Increased	2 (1.8)	8 (7.3)
Skin And Subcutaneous Tissue Disorders	2 (1.8)	5 (4.5)
Rash	1 (0.9)	3 (2.7)
Treatment-Emergent SAE		
Pneumonitis	2 (1.8)	8 (7.3)
Pneumonia	3 (2.8)	8 (7.3)

Source: Tables 12-1, 12-2, 12-3, 12-4, and 12-9 of CSR for Study 201.

The ER relationship for safety from the FDA reviewers' exploratory analysis based on the predicted mean daily AUC of the second week is also consistent with DR (Figure 9).

Figure 9: Plot of Probability of Experiencing a ≥ Grade 3 AE by Mean Daily Exposure of the Second Week



Source: FDA reviewer's analysis.

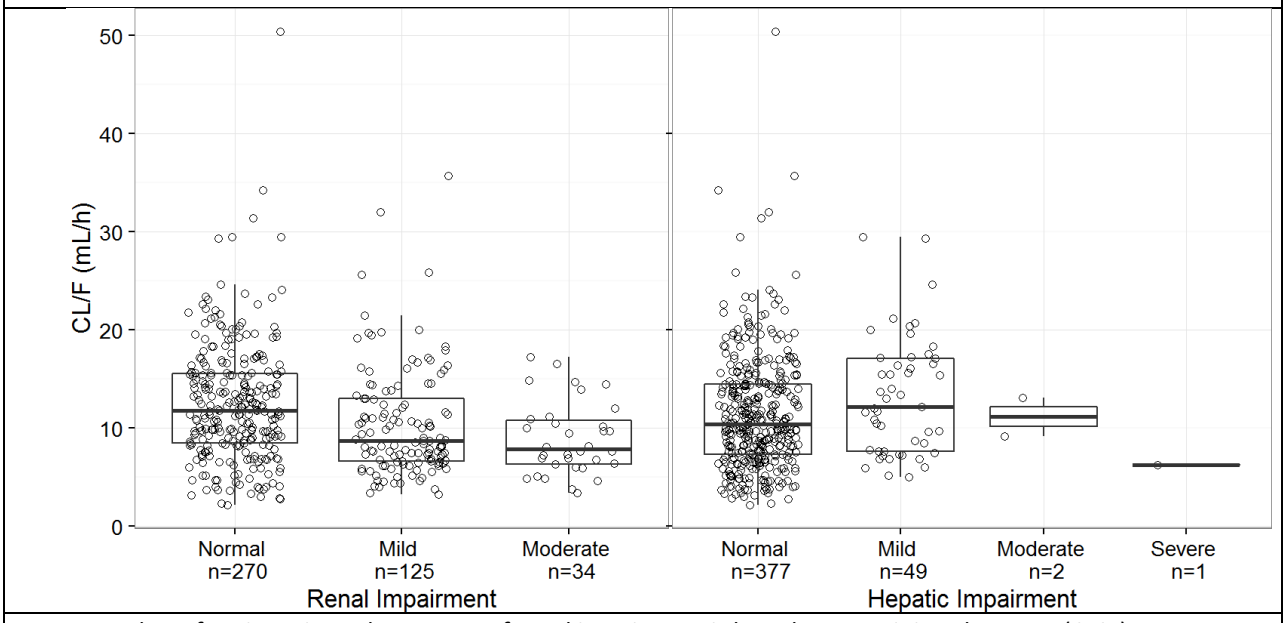
The proposed dose reduction strategy in the event of adverse reactions to the lowest acceptable dose of 60 mg QD is reasonable as the minimally effective brigatinib dose resulting in mean steady-state trough concentrations that exceed the IC_{50} for inhibition of EML4-ALK and 17 ALK secondary mutations associated with clinical resistance to crizotinib is 60 mg. Following 60 mg QD, the steady-state maximum concentrations exceed the IC_{90} for inhibition of EML4-ALK and 17 ALK secondary mutations associated with clinical resistance to crizotinib. In summary, the overall safety profile and low incidence of dose modification (20%) observed in Arm B support the use of the proposed higher dose (90/180 mg) with dose modification in the event of adverse reactions.

2.1.2 Do the findings based on PopPK analysis support clinical pharmacology labeling?

Yes, the PopPK analysis results support labeling the effect of hepatic/renal impairment on brigatinib exposure.

The dedicated clinical pharmacology studies about the effect of renal/hepatic impairment on brigatinib PK are ongoing, so the clinical pharmacological labeling about renal/hepatic impairment on brigatinib pharmacokinetics for this review cycle is based on PopPK analysis results shown in Figure 10. The figure indicated no clinically meaningful effect of mild to moderate renal impairment or mild hepatic impairment on the exposure of brigatinib.

Figure 10: The Effect of Organ Impairment on Brigatinib Clearance



Note: Number of patients in each category of renal impairment is based on creatinine clearance (CrCL).
Source: FDA reviewer's graphics based on applicant's final population pharmacokinetics analysis run3001.

3 Sponsor's Population Pharmacokinetics and E-R Analysis

3.1 PopPK Analysis

Reviewer note: *The information shaded in grey is copied from the Applicant's NDA submission.*

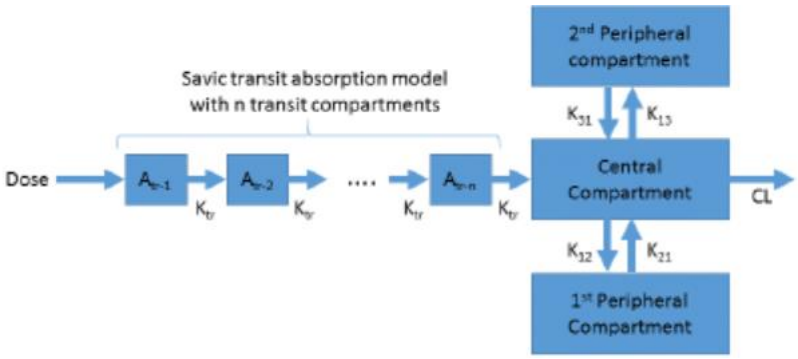
Data: The analysis dataset comprised of data from 443 subjects in total (338 patients and 105 healthy subjects) who contributed 5875 pharmacokinetic (PK) observations. Patients (N = 137) in study AP26113-11-101 received continuous daily doses of brigatinib in multiple 4-week cycles. Brigatinib was administered according to three treatment regimens in this study: continuous, once daily (QD) dosing (30-300 mg QD, with 300 mg only administered as a single dose on Cycle 1 Day 1 (C1D1)); twice daily (BID) dosing (60-120 mg BID); or QD at 180 mg after a lead in period of 7 days with 90 mg QD brigatinib. Dense PK sampling was carried out on Cycle 1 Day 1 (C1D1) up to 24 hours postdose and on Cycle 2 Day 1 (C2D1) up to 48 hours postdose, and additional trough measurements were obtained prior to dosing on Cycle 1 Days 8, 15, and 22 (C1D8, C1D15, C1D22). In total, 2539 PK samples collected in Study AP26113-13-101 were included in the analysis. In Study AP26113-13-102, subjects (N = 36) received single oral doses of 90, 120, or 180 mg brigatinib with dense PK sampling up to 72 hours postdose. In total, 504 PK samples collected in Study AP26113-13-102 were included in the analysis. In Study AP26113-13-103, subjects (N = 9) received a single oral of 180 mg brigatinib under fasting condition followed by dense PK sampling up to 72 hours postdose. Data obtained after intake of a high-fat meal was not included in this analysis. In total, 119 PK samples collected in Study AP26113-13-103 were included in the analysis. In Study AP26113-15-105, subjects (n = 60) received a single dose of either 90 mg or 180 mg brigatinib followed by dense PK sampling up to 120 hours postdose. Subjects were subsequently treated with brigatinib after coadministration with gemfibrozil, rifampin or itraconazole. Only PK samples obtained in treatment period 1 after the single dose of brigatinib alone were included in the analysis. In total, 1018 PK samples collected in Study AP26113-13-105 were included in the analysis. In Study AP26113-13-201, patients (N = 190) received either continuous QD doses of 90 mg brigatinib (Arm A) or continuous QD doses of 180 mg brigatinib after a 7 day lead in period with 90 mg brigatinib QD (Arm B). PK samples were obtained on C2D1, C3D1, C4D1 and C5D1. In total, 1695 PK samples collected in Study AP26113-13-201 were included in the analysis.

Methods: The pharmacokinetics (PK) of brigatinib was characterized by integrating all PK data into a nonlinear mixed effects model, describing the absorption, disposition, and elimination of brigatinib as well as the variability in PK between subjects and to examine the effect of covariates on the PK. The PopPK analysis was carried out using NONMEM (Version 7.3.0, ICON Development Solutions, Elicott City, MD, USA). The structural compartment model and random effect models were built starting from simple models, increasing in complexity until the data were adequately described without discernible lack of model fit or bias. Subject covariate relationships were examined in a stepwise procedure (stepwise covariate modelling (SCM) in Perl-speaks-Nonmem (PsN) (Lindbom et al., 2005)) to examine the impact of individual subject characteristics (age, body weight (WT), gender, race, creatinine clearance (CLcr), albumin and

alanine aminotransferase (ALT)) on PK model parameters. The final model was qualified by a numerical and graphical assessment of the goodness-of-fit (Figure 12) as well as a visual predictive check (VPC) and was subsequently used to derive exposure estimates for the patients included in Study AP26113-13-201 to allow for future exposure-response analyses.

Results: The brigatinib PK was best described by a three-compartment model with delayed, first-order absorption (Figure 11). A flexible transit compartment absorption model (TCAM) model (Savic et al., 2007) was included to describe variable absorption between subjects. The evaluation of possible effects of subject-specific characteristics on brigatinib PK showed that WT, age and albumin concentration had an impact on the PK of brigatinib. Race, gender, CLcr and ALT did not have an effect on brigatinib PK. There was also no difference observed in the brigatinib PK between the different studies in patients and healthy subjects.

Figure 11: Graphical Representation of the Final Population PK Model



Source: Figure 2 of Applicant's PopPK Report in Page 29.

The final PopPK parameters are listed in Table 55. Mean brigatinib apparent volume of distribution (V1/F) was 236 L and was identified to increase by 0.97% for every kg increase in WT. A subject of 100 kg is expected to have a 68.6% higher V1/F than a 50 kg subject.

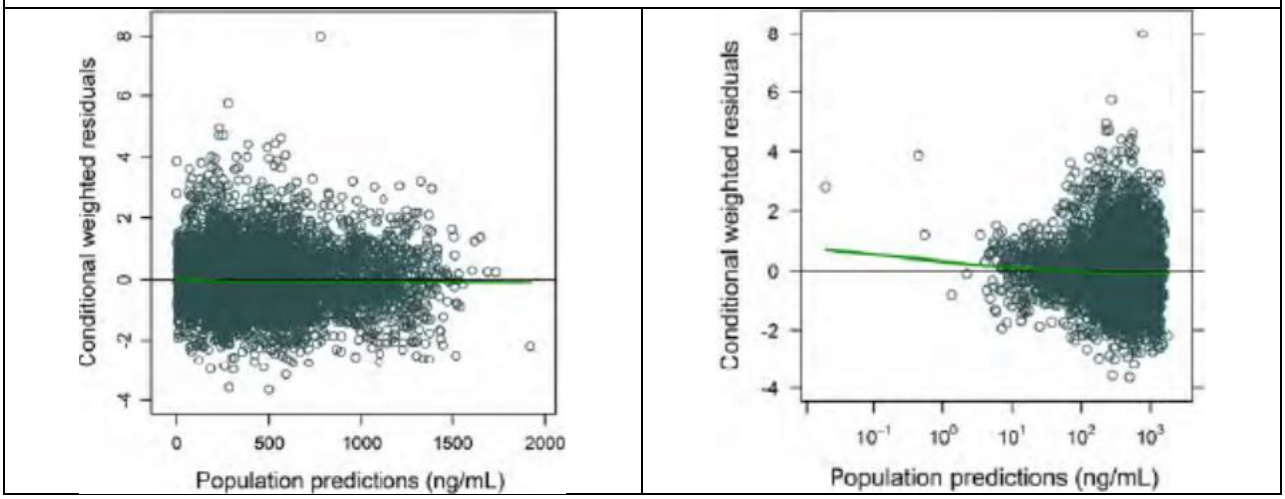
Table 55: Parameter Estimates of the Final PopPK Model

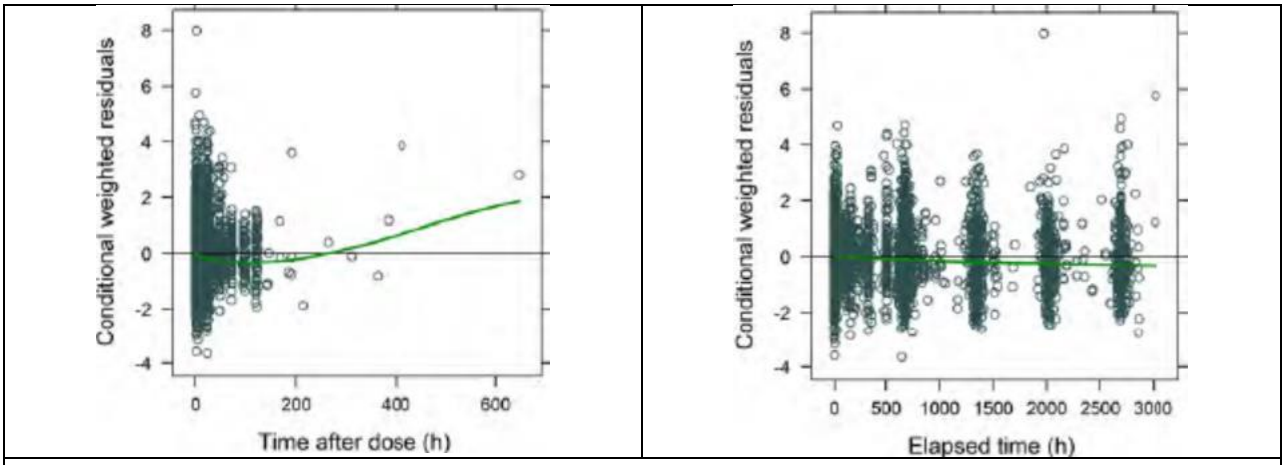
Parameter	Alias	Estimate	Relative SE (%)	95% CI
θ_1	CL/F (L·h^{-1})	10.4	2.7	(9.82 - 10.9)
θ_{10}	$\theta_{CL,age}$	-0.00651	23.4	(-0.00949 - -0.00353)
θ_{11}	$\theta_{CL,albumin}$	0.0165	15.6	(0.0115 - 0.0216)
θ_{12}	$\theta_{CL,weight}$	0.00732	15.2	(0.00515 - 0.0095)
θ_2	V_1/F (L)	236.	3.9	(218 - 254)
θ_{13}	$\theta_{V1,weight}$	0.00966	15.8	(0.00666 - 0.0127)
θ_3	NTR	2.74	.....	NC
θ_5	Q_1 (L·h^{-1})	9.44	6.7	(8.21 - 10.7)
θ_6	V_2 (L)	99.7	12.9	(74.5 - 125)
θ_7	Q_2 (L·h^{-2})	1.47	34.2	(0.486 - 2.46)
θ_8	V_3 (L)	73.8	18.1	(47.7 - 100)
θ_9	MTT (h)	0.845	3.6	(0.787 - 0.904)
$\omega_{1.1}$	ω^2_{CL}	0.211	6.9	(0.182 - 0.24)
$\omega_{2.1}$	$\omega^2_{CL,V1}$	0.178	10	(0.143 - 0.213)
$\omega_{2.2}$	ω^2_{V1}	0.333	9.5	(0.272 - 0.395)
$\omega_{3.3}$	ω^2_{MTT}	0.337	8.2	(0.283 - 0.391)
$\omega_{4.4}$	ω^2_{NTR}	1.07	.....	NC
θ_4	σ_{prop}	0.285	0.6	(0.282 - 0.288)

Source: Table 11 of Applicant's PopPK Report in Page 30.

Mean brigatinib apparent clearance (CL/F) was 10.4 L and was identified to increase by 0.73% for every kg increase in WT. A subject of 100 kg is therefore expected to have a 43.2% higher CL/F than a 50 kg subject resulting in 30.2% lower exposure (area under the curve between 0 and 24 hours postdose at steady state (AUC_{0-24})). Brigatinib CL/F was identified to decrease with increasing age by 0.65% per year. A 75 year old subject is expected to have a 29.2% lower CL/F compared to a 20 year old subject which corresponds to a 41.2 % higher AUC_{0-24} . Brigatinib CL/F is also expected to increase with increasing albumin concentrations. Across a normal range of albumin concentrations of 34 to 54 g/L, CL/F is expected to increase by 34.1%, resulting in a 25.4 % lower AUC_{0-24}.

Figure 12: Conditional Weighted Residuals (CWRES) versus Predictions (PRED), Time and Time after Dose for Final model





Source: Figure 5 of Applicant's PopPK Report in Page 32.

Conclusions: The brigatinib PK was best described by a three-compartment model with delayed, first-order absorption. A flexible TCAM model (mean transit time (MTT) of 0.845 h and number of transit compartments (NTR) equal to 2.74) was included to describe variable absorption between subjects. The evaluation of possible effects of subject-specific characteristics on brigatinib PK showed that WT, age and albumin concentration had an impact on the brigatinib PK. Mean brigatinib V1/F was identified to increase with WT, while mean brigatinib CL/F was identified to increase with WT and albumin concentration and decrease with age. Race, gender, CLcr and ALT did not have an effect on brigatinib PK. There was also no difference observed in the brigatinib PK between the different studies in patients and healthy subjects. Average predicted brigatinib exposure (AUC_{0-24} and maximum concentration (C_{max})) on C2D1 after administration of 90 or 180 mg brigatinib QD in Study AP26113-13-201 increased proportional with dose and is comparable to the exposure observed in Study AP26113-11-101.

3.2 E-R Analysis

Reviewer note: *The information shaded in grey is copied from the Applicant's NDA submission.*

Objective: the objective of exposure–response analyses is to evaluate the relationship between brigatinib exposure (represented by the geometric mean of trough concentrations at steady state) and selected efficacy and safety outcomes.

Sample Size: Data from 202 of the 219 treated patients with at least one trough concentration were available for the analysis geometric mean of the trough measurements with efficacy and safety parameters, with the exception of analyses of intracranial efficacy, which are performed on subsets of patients with brain metastases at baseline (see Section 3.2.2 for further detail on these subsets).

Methods of Analysis: The primary analysis methodology for this report is multivariate logistic regression with the outcome being the presence or absence of a treatment emergent adverse event of interest or an efficacy response. A preliminary univariate analysis using side-by-side boxplot of the geometric mean trough exposure by event is presented, along with the two-sided p-value from a 2-sample Wilcoxon test. For time-to-event safety and efficacy outcomes, for example progression free survival (PFS) or time to first serious adverse event (SAE), Kaplan-Meier methods are employed for analysis stratified by quartiles of the trough concentrations. Additionally, for time-to- event analyses, Cox regression models were performed to adjust for the covariates included in the multivariate logistic regression models. Analyses are based on a data cutoff of 29 February 2016 for all outcomes except for the Independent Review Committee (IRC) assessed intracranial response and PFS outcomes which are based on data received on 31 May 2016.

Covariate: A number of covariates present in all patients that are potentially related to the events are included in the logistic regression models. Covariates (along with their coded value in analysis) are: Sex (Female=0 or Male=1), Age at study entry (in years), Baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 v 1 and 2 combined), Prior chemotherapy use (Yes=1, No=0), Baseline tumor burden (common log of sum of longest diameter [SLD] of baseline target lesions), Time since diagnosis at study entry (in months) – patients with missing diagnosis date had the mean time since diagnosis for all patients in the study imputed.

Logistic Regression Analysis Methods: For each outcome, three sets of logistic regression analyses were performed: 1) Univariate logistic regression with intercept of the exposure parameter and each covariate, 2) Multivariate logistic regression (full model) which includes an intercept, the exposure parameter, and each covariate, and 3) Multivariate logistic regression (reduced model). From the full model to the reduced model, stepwise regression with backward selection was performed where the full model is fit and the least significant covariate is removed from the model until all covariates are significant at a 0.2 level. Note that the exposure parameter is not part of the backwards selection and is forced to remain in the model). The full results (including odds ratios for the covariates, p-values and the receiver operator characteristics [ROC] for the reduced multivariate model) of these models will be presented in text along with a plot of the reduced model with all remaining covariates fixed at their mean level. The plot will show varying exposure across the observed range and will include the 95% confidence interval on the predicted rate. Depending on the strength of the covariates, the model with covariates at the mean level is used for illustrative purposes, but may not reflect the rate seen in the entire population.

The logistic models have some limitations. Of note, they treat the exposure in a patient who discontinues early the same as a patient who has a much longer exposure without an event. To address the “static” nature of the logistic regression analysis, a Kaplan-Meier time-to-event analysis stratified by exposure quartiles was performed using the binary event variable and the time to the first event in a class or a censored time on treatment for patients without an event

and these will be presented by quartile of exposure, with the p-value for the log rank test. This test does not take into account the ordering of the quartiles, so additionally cox models are performed with the exposure variable as a covariate.

General Analysis and Presentation Considerations: For all outcomes the presentation will show the box plot showing the distribution of geometric mean trough concentrations in patients without and with the event/response. For all outcomes except for PFS, the summary of the three logistic regression models, and a plot of the reduced multivariate model will be presented. These plots are presented with the geometric mean trough (ng/mL) along the x-axis. The model prediction curve for the reduced model is displayed with covariates held at their mean value. The plot is overlaid with the proportion of events in each exposure quartile along with exact binomial 95% confidence intervals. For the PFS, SAE, and Grade 3 or higher AEs, Kaplan-Meier plots of the time to event stratified by exposure quartile will be included, and if differences are noted across the quartiles in the stratified log rank test, summaries of the Cox regression model will also be included. Models not presented in text will be included in the appendix.

Results: The representative exposure-response results are presented in Table 56 through Table 59, and Figure 13 and Figure 14.

Table 56: Distribution of Covariates, Time on Study, Starting Dose Cohort by Geometric Mean Trough Concentration , and Major Efficacy Results (N=202)

Variable	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile
Quartile Midpoint (ng/mL)	110	244.5	427.6	1076.3
Interval (ng/mL)	43.7 to 176.3	176.3 to 312.6	312.6 to 542.5	542.5 to 1610.2
Number of Patients	51	50	50	51
Sex (% Male)	58.8	38	36	35.3
Baseline ECOG PS 0 or 1 (%)	66.7	66	76	66.7
Mean Age (years)	49	51.9	53	56.9
Prior Chemotherapy Use (%)	70.6	68	82	76.5
Log BSLD (mean)	1.7	1.6	1.6	1.7
Mean Time Since Diagnosis (mo)	27	32.5	32.5	34.6
Mean Time on Study (mo)	8	8.9	9.1	8.2
Arm A	41	32	19	10
Arm B	10	18	31	41
INV Confirmed ORR	49%	54%	64%	49%
Median INV PFS (mo)	8.9	15.6	Not Reached	11.8
IRC Confirmed Brain ORR	33.30%	66.70%	55.60%	100%

Source: Tables 4-1 and 4-2 of applicant's exposure-response analysis report.

Table 57: Summary of Univariate and Multivariate Logistic Regression Analyses of Confirmed Objective Response (N=202)

	Univariate Analyses		*Multivariate (Full)*		*Multivariate (Reduced)*		Unit of Odds Ratio
Covariate	Odds Ratio	p-value	Odds Ratio	p-value	Odds Ratio	p-value	
Geometric Mean Trough	0.97	0.5638	0.96	0.4782	0.97	0.5151	100
Male	0.93	0.8044	0.95	0.876			1
Age (years)	1.06	0.5849	1.08	0.4971			10
ECOG PS (1/2 vs 0)	1	0.9977	1.06	0.8425			1
Prior Chemotherapy Use (Yes vs No)	0.82	0.5313	0.65	0.2227			1
Log Sum Baseline Target Lesions	0.45	0.0693	0.55	0.1981	0.55	0.1896	1
Time Since Diagnosis in Months	1.01	0.0571	1.01	0.072	1.01	0.0998	1

Source: Tables 4-3 of applicant's exposure-response analysis report.

Table 58: Summary of Univariate and Multivariate Logistic Regression Analyses of IRC-Assessed Confirmed Intracranial Response (Subset with Measurable Baseline Brain Metastases) (N=202)

	Univariate Analyses		*Multivariate (Full)*		*Multivariate (Reduced)*		Unit of Odds Ratio
Covariate	Odds Ratio	p-value	Odds Ratio	p-value	Odds Ratio	p-value	
Geometric Mean Trough	2.25	0.0255	2.46	0.1116	2.61	0.0536	100
Male	0.4	0.2006	0.35	0.4151			1
Age (years)	1.09	0.7216	1.06	0.8825			10
ECOG PS (1/2 vs 0)	0.48	0.3225	2.03	0.5749			1
Prior Chemotherapy Use (Yes vs No)	1.77	0.4412	12.63	0.0831	6.84	0.1128	1
Log Sum Baseline Target Lesions	0.06	0.0404	0	0.0131	0	0.0108	1
Time Since Diagnosis in Months	0.99	0.4177	0.89	0.0093	0.9	0.0159	1

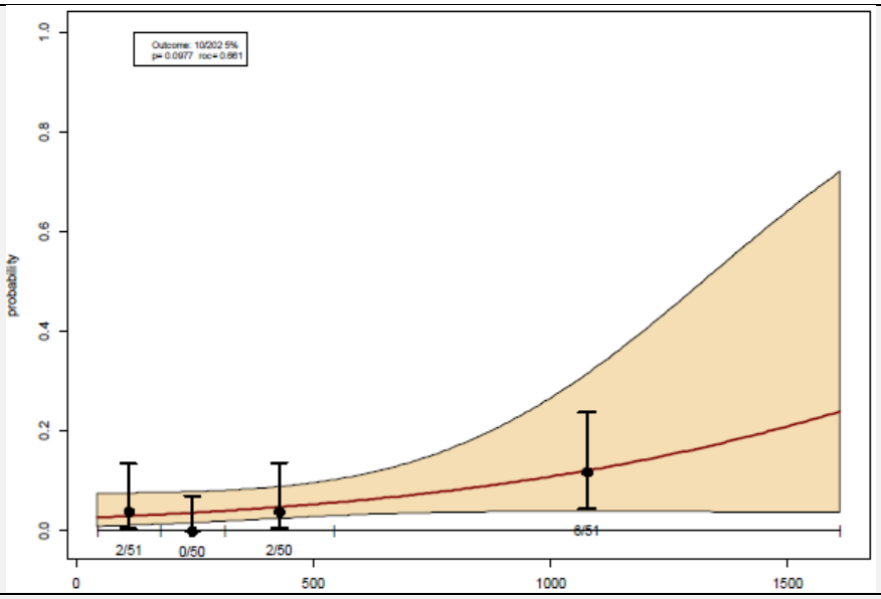
Source: Tables 4-4 of applicant's exposure-response analysis report.

Table 59: Distribution of Covariates, Time on Study, Starting Dose Cohort by Geometric Mean Trough Concentration, and Major Efficacy Results (N=202)

Variable	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile
Dose Interruption ≥7 Days	23.50%	20%	20%	21.60%
Dose Reduction Due to AE	11.80%	22%	8%	17.60%
Any Dose Modification	25.50%	24%	24%	25.50%
Any Serious Adverse Event	37.30%	34%	30%	37.30%
Any Grade 3+ TEAE	51%	40%	38%	51%

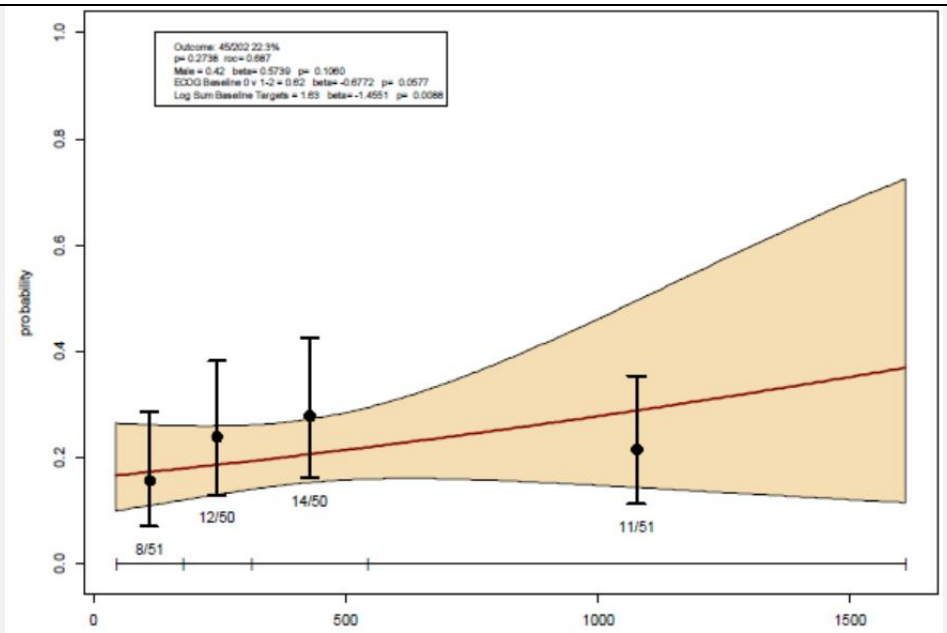
Source: Table 4-6 of applicant's exposure-response analysis report.

Figure 13: Plot of Probability of Experiencing an Increased Glucose or Insulin AEs by Geometric Mean of Trough Concentrations (ng/mL)



Source: Figure 4-36 of applicant's exposure-response analysis report.

Figure 14: Plot of Probability of Experiencing an Increased CPK AEs by Geometric Mean of Trough Concentrations (ng/mL)



Source: Figure 4-38 of applicant's exposure-response analysis report.

Summary: Table 60 summarizes the findings of the logistic regression analyses for the outcomes studied using the geometric mean of the trough concentrations on day 1 of Cycles 2, 3, 4, and 5 in the reduced multivariate model. There were no significant difference in any of the reduced multivariate models; however, trends (p<0.25) are noted with yellow shading.

Table 60: Overall Summary of Primary Logistic Regression Results from Reduced Multivariate Model for Geometric Mean Trough Concentration (N=202)

Event	Number of Events or Responses	Odds Ratio (per 100 ng/mL increase)	P-value	Other Statistically Significant Covariates
Investigator-Assessed Confirmed ORR	109/202	0.97	0.5151	
Investigator-Assessed PFS Event	73/202	1	0.9681	Log SLD of Target Lesions (more PFS events) Time since Diagnosis (fewer PFS events)
IRC Confirmed Intracranial Objective Response (Measurable Baseline Brain Metastases)	23/36	2.61	0.0536	Log SLD of Target Lesions (lower rates) Time Since Diagnosis (lower rate)
IRC Intracranial PFS (Any Baseline Brain Metastases)	36/140	0.89	0.2007	
Dose Interruption (7 or more days)	43/202	0.96	0.5127	
Dose Reduction due to AE	30/202	0.99	0.9083	
Dose Modification	50/202	1.02	0.7099	
Any SAE	70/202	1	0.9761	Log SLD of Target Lesions (higher rate)
Any Grade 3 or Higher AE	91/202	1	0.9431	Age (higher rate)
Gr 2 or Higher Hypertension Events	27/202	1.09	0.2155	
Gr 2 or Higher Hepatic Events	10/202	1.08	0.4707	
ALT Increased AE	19/202	0.96	0.6559	
AST Increased AE	25/202	1.02	0.7645	
ALP Increased AE	6/202	1.14	0.3174	
Increased Lipase	21/202	1.05	0.5438	
Increased Amylase	25/202	1.05	0.4881	Prior Chemotherapy (higher rate)
Glucose or Insulin Increased AE	10/202	1.17	0.0977	
Increased CPK AE	45/202	1.07	0.2738	Log SLD of Target Lesions (lower rate)
Gr 2 or Higher GI Events	37/202	1.07	0.2899	
Gr 2 or Higher Skin Events	15/202	1.12	0.213	

Note: Yellow shading represents trend (p<0.25).
Source: Table 5-1 of applicant's exposure-response analysis report.

Conclusion: These analyses examined the relationship of the geometric mean of trough concentrations of brigatinib at the beginning of Cycles 2, 3, 4, and 5 to efficacy and safety endpoints in an ALK+ NSCLC population. The covariates of gender, age, baseline ECOG PS, use of prior chemotherapy regimens, baseline tumor burden, and time since diagnosis at study entry were also examined. The efficacy endpoints analyzed included investigator-assessed confirmed ORR and PFS, IRC-assessed intracranial objective response (in patients with measurable

baseline brain metastases), and IRC-assessed intracranial PFS (in patients with any baseline brain metastases). The safety outcomes analyzed included dose interruption of 7 or more days, dose reduction due to AE, any dose modification, any treatment emergent SAE, any Grade 3 or higher TEAE, Grade 2 or higher hypertension AE, Grade 2 or higher hepatic event AE, any grade ALT increased AE, AST increased AE, ALP increased AE, lipase increased AE, amylase increased AE, blood insulin or blood glucose increased AE, CPK increased AE, Grade 2 or higher gastrointestinal AE, and Grade 2 or higher skin and subcutaneous tissue disorder AE.

- Most patient characteristics used as covariates were generally similar across the quartiles. The percentage of males was higher in the lowest exposure quartile, and age and time since diagnosis increased with increasing exposure. Time on study was generally similar across the quartiles with the middle 2 quartiles having a slightly longer mean time on study. As expected, patients with lower exposure were more likely to be in Arm A (90 mg QD) and conversely those with higher exposure more likely to be in Arm B (90 mg QD → 180 mg QD).
- There was a significant association between geometric mean trough concentration and IRC- assessed intracranial objective response in patients with measurable baseline disease in the univariate analysis and a strong trend (p=0.0536) towards an association in a reduced multivariate model. The multivariate model may have been overspecified in this relatively small subset (see Section 4.2.3). The Cox regression model for time to IRC-assessed intracranial PFS also trended towards improvement with higher exposure.
- There were not consistent trends in association between geometric mean trough concentrations and the primary endpoint of investigator-assessed confirmed ORR or PFS. Confirmed ORR was 49% or higher in all four quartiles, and PFS ranged from 8.9 months (in the lowest quartile) to not yet reached. Generally the third quartile of exposure had the best nominal response rate and PFS.
- Higher geometric mean trough concentrations was associated with a nonsignificant trend towards increase in some events including Grade 2 or higher skin events, increased glucose or insulin AEs of any grade, and Grade 2 or higher hypertension events.
- Other adverse events studied were not significantly associated with increased exposure. These analyses could understate the association as the event could have occurred prior to the timing of the PK evaluations in some patients.

Study AP26113-13-201 randomized patients to either 90 mg QD or 180 mg QD (with 7 day lead in at 90 mg QD). Overall, the findings in this analysis are generally consistent with those seen when comparing the higher dose arm to the lower dose arm in that study (improved intracranial when comparing the higher dose arm to the lower dose arm in that study (improved intracranial efficacy, some higher adverse event rates including GI events and hypertension). Other outcomes where differences were observed comparing the randomized arms in that study were not associated with increasing geometric mean trough concentrations in this analysis. These include investigator-assessed PFS as well as dose modifications and increased CPK AEs. This may be due to limitations of the analyses in this report including a relatively small number of PK samples, variability in the timing of the trough concentrations,

intrapatient variability in concentrations, and the timing of the sampling relative to the outcome.

Overall, these results demonstrate high response rates and durable responses along with an acceptable safety profile across the range of exposures seen with the two dose regimens in this study.

Reviewer's Comments: *The clearance of brigatinib showed some extent of time-dependency as indicated by the declining loess curve of CWRES-Time plot Figure 12; the brigatinib clearance appeared to increase with time, resulted in a population CL of 3-5% higher at steady-state than baseline. This may have introduced uncertainty or variation to the exposure-response analysis when geometric mean trough concentration of Cycles 2-5 was used as exposure metrics.*
The exposure-response results did not reflect the dose-response for either efficacy or safety observed in Study 201. We conducted independent exploratory analyses to further investigate the ER relationship (4.4.2).

4 Reviewer's Analysis

4.1 Introduction

The PopPK dataset initially submitted by the Applicant had 2 defects:

1. Concentration data for 11 patients of Study 201 were missing without explanation.
2. Some patients of Study 201 received BID doses, but not reflected in the PopPK dataset.

After an information request, the Applicant submitted revised dataset "nm_pk_26oct2016.csv" and corresponding final model "run3001". The FDA reviewer's PopPK analysis was conducted to confirm the analysis, and evaluate the effect of renal/hepatic impairment on brigatinib clearance by linking the output with "NPKOCT16.xpt" to provide information for labeling.

The Applicant's exposure-efficacy relationship appeared to be inconsistent with the observed dose response relationship. The FDA reviewer conducted exposure-efficacy analysis in two ways:

1. Using the mean exposure from Day 1 to the response date for ORR, PFS and OS.
2. Using dynamic exposure (for a period of 1 day, 1 week or several weeks) immediately prior to each study day.

4.2 Objectives

The FDA reviewer's analyses were conducted to:

1. Confirm Applicant's updated PopPK analysis and provide information for clinical pharmacology labeling.
2. Explore the E-R relationship for efficacy using new exposure variables.

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 61.

Table 61: Analysis Data Sets	
Name	Link to EDR
adae.xpt	\\cdsesub1\evsprod\nda208772\0014\m5\datasets\ap26113-13-201\analysis\adam\datasets\adae.xpt
adeff.xpt	\\cdsesub1\evsprod\nda208772\0005\m5\datasets\ap26113-13-201\analysis\adam\datasets\adeff.xpt
adexd.xpt	\\cdsesub1\evsprod\nda208772\0014\m5\datasets\ap26113-13-201\analysis\adam\datasets\adexd.xpt
adlb.xpt	\\cdsesub1\evsprod\nda208772\0014\m5\datasets\ap26113-13-201\analysis\adam\datasets\adlb.xpt
adls.xpt	\\cdsesub1\evsprod\nda208772\0005\m5\datasets\ap26113-13-201\analysis\adam\datasets\adls.xpt
adpc.xpt	\\cdsesub1\evsprod\nda208772\0005\m5\datasets\ap26113-13-201\analysis\adam\datasets\adpc.xpt
adsl.xpt	\\cdsesub1\evsprod\nda208772\0014\m5\datasets\ap26113-13-201\analysis\adam\datasets\adsl.xpt
nm_pk_26oct2016.csv (final NONMEM dataset)	\\cdsesub1\evsprod\nda208772\0016\m5\datasets\ariad-bri-02\analysis\adam\programs\nm_pk_26oct2016_csv.txt
run3001 (final NONMEM code)	\\cdsesub1\evsprod\nda208772\0015\m5\datasets\ariad-bri-02\analysis\adam\programs\run3001_lst.txt
npkoct16.xpt (for renal and hepatic impairment data)	\\cdsesub1\evsprod\nda208772\0015\m5\datasets\ariad-bri-02\analysis\adam\datasets\npkoct16.xpt

4.3.2 Software

NONMEM (v7.3) and R (v3.2.2) were used for the FDA reviewer's analysis.

4.4 Results

4.4.1 PopPK Analysis Results

The Applicant's final PopPK analysis (run3001) was confirmed, and the effect of renal/hepatic impairment is presented in Figure 10.

4.4.2 Exposure-Efficacy Analysis

The study was not stratified for baseline factors (e.g., ECOG, baseline tumor size, study region and race). There are 11% more ECOG0 patients in Arm B than Arm A (41% vs 30%) and associated with this, the mean baseline tumor size of Arm B is 18 mm smaller than Arm A, and mean tumor lesion numbers is also smaller than Arm A. All these may have favored the efficacy

result of Arm B. On the contrary, there were 8% more Asian patients in Arm A than Arm B (35% vs 27%), which may have favored the efficacy result of Arm A to some extent. In general, ECOG and study region are randomization factors in a non-small cell lung cancer (NSCLC) efficacy study, but they were somehow not considered in Study 201 (b) (4) of brigatinib.

Factor	ARM A (90 MG)	ARM B (90/180 MG)
Asia-Pacific/Europe-North-America	35/65	26/74
White/Asian/Black-NA	64/35/1	69/27/4
Brain Tumor Y/N	29/71	33/67
ECOG 0/1-or-2	30/70	41/59
Crizotinib R/NR	62/38	65/35
BASETMR (mm)	66 ± 46	48 ± 35
NUMSITES	3.72 ± 1.47	3.39 ± 1.29
Source: FDA reviewer's analysis.		

Dynamic exposures-response analysis for PFS and OS

Using dynamic exposures, a positive exposure-efficacy relationship was found for PFS and OS. Daily AUC was implemented based on daily dose from file "adexd.xpt" and patient clearance from population PK analysis by simple calculation.

$$AUC_{day1-dayN} = \frac{Cumulative\_Dose}{CL}$$

$$AUC_{dayi} = AUC_{day1-day(i+1)} - AUC_{day1-dayi}$$

The log value of daily AUC (i.e., lgAUC1D) was selected based on AIC value comparison of the cox proportional hazard modeling on 10 exposure metrics. The 10 exposure metrics explored were daily AUC (AUC1D), weekly AUC (AUC1W), AUC every 3 weeks (AUC2W), AUC every 3 weeks (AUC3W), AUC every 4 weeks (AUC4W), and their log transformed values (lgAUC1D, lgAUC1W, lgAUC2W, lgAUC3W, lgAUC4W). The AIC value of lgAUC1D was the smallest among the 10 metrics for both OS and PFS.

OS hazard ratio (95%CI) of Arm B vs Arm A was estimated to be 0.954 (0.936, 0.971) based on model:
lgf1d<-coxph(Surv(START, STOP,EVENT)~lgAUC1D + ECOGBLN, data=dta)

The OS hazard ratio was estimated to be 0.956 (0.940, 0.972) based on univariate model:
lgf1d<-coxph(Surv(START, STOP,EVENT)~lgAUC1D, data=dta)

PFS hazard ratio (95%CI) of Arm B vs Arm A was estimated to be 0.975 (0.969, 0.981) based on model:
lgf1d<-coxph(Surv(START, STOP,EVENT)~lgAUC1D+NUMSITES+ BASEDIAM,, data=dta)

The PFS hazard ratio was estimated to be 0.976 (0.970, 0. 982) based on univariate model:
lgf1d<-coxph(Surv(START, STOP,EVENT)~lgAUC1D, data=dta)

Exposure-efficacy analysis based on accumulated dose

Mean daily AUC to response date ($AUC_{2ResponseDate}$) was implemented based on daily dose from file "adexd.xpt", response data "adeff.xpt", and patient clearance from population PK analysis by simple calculation.

$$AUC_{2\,\mathrm{Re}sponseDate} = \frac{Cumulative\_Dose\_to\_\mathrm{Re}sponse\_Date}{CL}$$

The binominal logistic regression model was implemented to OR, and COXPH models were implemented to OS/PFS data with covariates for study region (REGION and associated RACE) and disease condition (DIAGBRN + PCBRESPN + ECOGBLN + NUMSITES + BASEDIAM) considered. The results are listed in Table 53. DIAGBRN is the brain metastases at study entry with values "Yes" or "No"; PCBRESPN is the best response to prior crizotinib regimen with value 1 for complete response or partial response and 0 for otherwise; ECOGBLN is the baseline ECOG performance status with values of 0, 1 or 2; NUMSITES is the number of metastatic sites at study entry with values of 1 to 9; and BASEDIAM is the sum of diameters (in mm) of target lesions at baseline.

4.4.3 Exposure-Safety Analysis

Mean daily AUC to from Day 8 to Day 14 was implemented based on daily dose data from file "adexd.xpt" and patient clearance (CL) from population PK analysis by simple calculation.

$$Mean\_Daily\_AUC = \frac{Cumulative\_Dose\_from\_Day8\_to\_Day14}{7*CL}$$

The binominal logistic regression model was implemented to adverse event (AE) data with Mean_Daily_AUC as predictor. The result for Grade 3 and higher AE is shown in Figure 9.

14 Division Director (DHOT)

I concur.

X

John K. Leighton, Ph.D.

15 Division Director (OCP)

I concur.

X

NAM Atiqur Rahman, Ph.D.

16 Division Director (OB)

I concur.

X

Rajeshwari Sridhara, Ph.D.

17 Division Director (Clinical)

I concur with the review teams' and consultants' recommendations that the NDA for brigatinib be approved, under the provisions of 21 CFR 314.510 Subpart H, for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. My recommendation is based on the totality of evidence submitted to the NDA, including treatment effects on primary and secondary endpoints and identified adverse reactions, and the size and quality of the trials contributing data to this application.

Substantial evidence of the safety and effectiveness of brigatinib is primarily derived from the results of an adequate and well-controlled, randomized, non-comparative, international trial (ALTA) investigating two brigatinib dosing regimens in adult patients with locally advanced or metastatic ALK-positive non-small cell lung cancer who had progressed on or were intolerant to crizotinib. The trial required patients to have documented ALK rearrangement based on an FDA-approved test or a different test with adequate archival tissue to confirm ALK rearrangement by the Vysis® ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit test. The ALTA trial demonstrated clinically meaningful overall response rates by both investigator and independent central reviewer assessment in the 110 patients randomized to receive the brigatinib dose proposed in product labeling (90 mg orally daily for the first 7 days, followed by 180 mg daily). A slightly lower but still clinically meaningful overall response rate was observed in 112 patients randomized to the lower dose arm (90 mg daily). Additionally, these overall responses were durable and consistent across relevant patient subsets.

Given the large magnitude of the overall response rates observed, the lower bounds of the 95% confidence intervals for the overall response rates for both treatment arms exclude a response rate that would not be considered clinically meaningful (Table 62).

Table 62: ALTA Efficacy Results

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

Abbreviations: CI =confidence interval

Additionally, durable intracranial objective responses as assessed by independent neuroradiology review were observed in a substantial proportion of patients with measurable central nervous system (CNS) metastases at baseline.

These durable systemic and CNS responses are reasonably likely to predict a clinical benefit that represents a meaningful advantage over available therapy in patients with metastatic ALK-positive metastatic NSCLC who have progressed on prior crizotinib therapy, given the serious and life-threatening nature of this disease. Most of the adverse reactions to brigatinib are manageable with supportive care or dose modification. These include risks of hypertension, bradycardia, creatine phosphokinase (CPK) elevation, pancreatic enzyme elevation, and hyperglycemia. Other potentially serious but rare adverse reactions are pulmonary toxicity (including fatal pneumonitis) and visual toxicities. Despite the risks of these adverse reactions, brigatinib has a favorable risk:benefit assessment in light of the magnitude and durability of responses observed in patients treated with brigatinib in the ALTA trial and the risks associated with alternative treatments such as cytotoxic chemotherapy and PD-1 inhibitors that, although not approved specifically for patients with refractory ALK-positive metastatic NSCL, may be used in this population.

As a condition of accelerated approval, one or more clinical trials will be required to further verify and describe the clinical benefit of brigatinib in patients with metastatic ALK-positive NSCLC. ARIAD has agreed to submit data from Study AP25113-13-301 (“Study 301”), a multicenter open label randomized study of brigatinib versus crizotinib in patients with ALK-

positive advanced non-small cell lung cancer to fulfill the postmarketing requirement required under the accelerated approval regulations, 21 CFR 314.510.

X

Martha Donoghue, M.D.
Acting Associate Director, DOP2

18 Office Director (or designated signatory authority)

This application was reviewed under the auspices of the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

My signature below also represents the approval decision of this application under CDER.

Richard Pazdur, M.D.

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/s/

LEAH S HER
04/28/2017

M A GOHEER
04/28/2017

EMILY F WEARNE
04/28/2017

WHITNEY S HELMS
04/28/2017

RUBY LEONG
04/28/2017

HONGSHAN LI
04/28/2017

HONG ZHAO
04/28/2017
I concur.

JIANG LIU
04/28/2017

THOMAS T LY
04/28/2017

KUN HE
04/28/2017

MARGIT N HORIBA
04/28/2017

STEVEN J LEMERY

04/28/2017

JOHN K LEIGHTON
04/28/2017

NAM ATIQUR RAHMAN
04/28/2017

RAJESHWARI SRIDHARA
04/28/2017

MARTHA B DONOGHUE
04/28/2017

RICHARD PAZDUR
04/28/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

MEMORANDUM

DATE: April 17, 2017

FROM: Martha Donoghue, MD
Supervisory Acting Associate Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research

SUBJECT: Acting Associate Division Director Summary Review

TO: NDA 208772

Please refer to the Integrated Multidisciplinary Review of NDA 208772 for a detailed review of this application.

I concur with the review team's and consultants' recommendations that the NDA for brigatinib be approved, under the provisions of 21 CFR 314.510 Subpart H, for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. My recommendation is based on the totality of evidence submitted to the NDA, including treatment effects on primary and secondary endpoints and identified adverse reactions, and the size and quality of the trials contributing data to this application.

Substantial evidence of the safety and effectiveness of brigatinib is primarily derived from the results of an adequate and well-controlled, randomized, non-comparative, international trial (ALTA) investigating two brigatinib dosing regimens in adult patients with locally advanced or metastatic ALK-positive non-small cell lung cancer who had progressed on or were intolerant to crizotinib. The trial required patients to have documented ALK rearrangement based on an FDA-approved test or a different test with adequate archival tissue to confirm ALK rearrangement by the Vysis® ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit test. The ALTA trial demonstrated clinically meaningful overall response rates by both investigator and independent central reviewer assessment in the 110 patients randomized to receive the brigatinib dose proposed in product labeling (90 mg orally daily for the first 7 days, followed by 180 mg daily). A slightly lower but still clinically meaningful overall response rate was observed in 112 patients randomized to the lower dose arm (90 mg daily). Additionally, these overall responses were durable and consistent across relevant patient subsets.

Given the large magnitude of the overall response rates observed, the lower bounds of the 95% confidence intervals for the overall response rates for both treatment excludes a response rate that would not be considered clinically meaningful (Table 1).

Table 1: ALTA Efficacy Results

Efficacy parameter	IRC Assessment		Investigator Assessment	
	90 mg once daily (N=112)	90→180 mg once daily (N=110)	90 mg once daily (N=112)	90→180 mg once daily (N=110)
Objective Response Rate (95% CI)	48% (39-58)	53% (43-62)	45% (35-54)	54% (44-63)
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Partial Response, n (%)	50 (45%)	53 (48%)	49 (44%)	55 (50%)
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Abbreviations: CI =confidence interval

Additionally, durable intracranial objective responses as assessed by independent neuroradiology review were observed in a substantial proportion of patients with measurable central nervous system (CNS) metastases at baseline.

These durable systemic and CNS responses are reasonably likely to predict a clinical benefit that represents a meaningful advantage over available therapy in patients with metastatic ALK-positive metastatic NSCLC who have progressed on prior crizotinib therapy, given the serious and life-threatening nature of this disease. Most of the adverse reactions to brigatinib are manageable with supportive care or dose modification. These include risks of hypertension, bradycardia, creatine phosphokinase (CPK) elevation, pancreatic enzyme elevation, and hyperglycemia. Other potentially serious but rare adverse reactions are pulmonary toxicity (including fatal pneumonitis) and visual toxicities. Despite the risks of these adverse reactions, brigatinib has a favorable risk:benefit assessment in light of the magnitude and durability of responses observed in patients treated with brigatinib in the ALTA trial and the risks associated with alternative treatments such as cytotoxic chemotherapy and PD-1 inhibitors that, although not approved specifically for patients with refractory ALK-positive metastatic NSCL, may be used in this population.

As a condition of accelerated approval, one or more clinical trials will be required to further verify and describe the clinical benefit of brigatinib in patients with metastatic ALK-positive NSCLC. Ariad has agreed to submit data from Study AP25113-13-301 ("Study 301"), a multicenter open label randomized study of brigatinib versus crizotinib in patients with ALK-positive advanced non-small cell lung cancer to fulfill the postmarketing requirement required under the accelerated approval regulations, 21 CFR 314.510.

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/s/

MARTHA B DONOGHUE
04/17/2017

Office of Hematology and Oncology Products Memorandum

Application Type	NDA
Application Number(s)	208772
Priority or Standard	Priority
Submit Date(s)	August 29, 2016
Received Date(s)	August 29, 2016
PDUFA Goal Date	April 29, 2017
Division/Office	DOP2/OHOP
CDTL Review Completion Date	24 Mar 2017
Established Name	Brigatinib
(Proposed) Trade Name	ALUNBRIG
Pharmacologic Class	Kinase inhibitor
Applicant	ARIAD Pharmaceuticals, Inc.
Formulation(s)	Tablet
Dosing Regimen	90 mg orally once daily for the first seven days, then 180 mg orally once daily
Applicant Proposed Indication(s)/Population(s)	ALUNBRIG is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.
Recommendation on Regulatory Action	Accelerated approval

The Cross-Discipline Team Leader review is complete and has been added to the NDA Multi-Disciplinary Review and Evaluation which will be uploaded into DAARTS when it is finalized. I recommend accelerated approval under 21 CFR 314.510 Subpart H for brigatinib for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. This recommendation is contingent upon reaching final agreement on product labeling and PMCs/PMRs. Please refer to the Multi-disciplinary Review and Evaluation for additional details.

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/s/

STEVEN J LEMERY
03/24/2017

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES-MEMO

NDA Serial Number:	208772
Drug Name:	Alunbrig® (brigatinib)
Indication(s):	Anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) in patients that have progressed on or are intolerant to crizotinib
Applicant:	ARIAD
Submission Date(s):	August 29, 2016
PDUFA Goal date:	April 28, 2017
Review Priority:	Priority
Biometrics Division:	Division of Biometrics 5 (DBV)
Statistical Reviewer:	Thomas Ly, Ph.D
Concurring Reviewers:	Kun He, Ph.D Rajeshwari Sridhara, Ph.D.
Medical Division:	Division of Oncology Products 2 (DOP2)
Clinical Team:	Naomi Horiba, M.D. Steven Lemery, M.D. Patricia Keegan, M.D.
Project Manager:	Leah Her, MS, PMP

The statistical review is complete and has been added to the Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for additional details. From a statistical standpoint, the NDA is acceptable to support approval provided that the Applicant and the FDA reach an agreement regarding the labeling language.

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/s/

THOMAS T LY
02/02/2017

KUN HE
02/02/2017

RAJESHWARI SRIDHARA
02/10/2017

MEMORANDUM

DATE: April 26, 2017
FROM: M. Naomi Horiba
THROUGH: Steven Lemery
TO: File for NDA 208772 brigatinib (ALUNBRIG)
Re: Amendment to Clinical Review (Feb. 7, 2017) for NDA 208772

An error was made listing the statute for accelerated approval. It should read "21 CFR 314.510 Subpart H", not "21 CFR part 601, subpart E". The correct memo in its entirety is below:

Ariad Pharmaceuticals submitted NDA 208772 for brigatinib (ALUNBRIG) for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. The clinical review of safety and efficacy is complete and has been added to the NDA/BLA Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. The clinical reviewers recommend the accelerated approval (**21 CFR 314.510 Subpart H**) of brigatinib for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. Refer to the Multi-disciplinary Review and Evaluation for additional details.

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/s/

MARGIT N HORIBA
04/26/2017

STEVEN J LEMERY
04/26/2017

MEMORANDUM

DATE: February 7, 2017
FROM: M. Naomi Horiba
THROUGH: Steven Lemery
TO: File for NDA 208772 brigatinib (ALUNBRIG)
Re: Clinical Review for NDA 208772

Ariad Pharmaceuticals submitted NDA 208772 for brigatinib (ALUNBRIG) for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. The clinical review of safety and efficacy is complete and has been added to the NDA/BLA Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. The clinical reviewers recommend the accelerated approval (21 CFR part 601, subpart E) of brigatinib for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. Refer to the Multi-disciplinary Review and Evaluation for additional details.

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/s/

MARGIT N HORIBA
02/07/2017

STEVEN J LEMERY
02/07/2017

MEMORANDUM

Date: January 23, 2017

From: M Anwar Goheer, PhD
Pharmacology Reviewer
Division of Hematology Oncology Toxicology for Division of Oncology Products 2

And

Emily F. Wearne, PhD
Pharmacology Reviewer
Division of Hematology Oncology Toxicology for Division of Oncology Products 2

Through: Whitney S. Helms, Ph.D.
Supervisory Toxicologist
Division of Hematology Oncology Toxicology for Division of Oncology Products 2

To: File for NDA #208772
Alunbrig ™ (Brigatinib)

Re: Approvability of Pharmacology and Toxicology

ARIAD Pharmaceuticals Inc. submitted NDA 208772 for Alunbrig™ (brigatinib) for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

Alunbrig™ is a kinase inhibitor. The nonclinical review is complete and has been added to the Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for additional details. There are no outstanding issues from a pharmacology/toxicology perspective that would prevent approval of this application.

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/s/

M A GOHEER
01/23/2017

EMILY F WEARNE
01/23/2017

WHITNEY S HELMS
01/25/2017

Office of Clinical Pharmacology Memo	
NDA	208772
Link to EDR	\\CDSESUB1\evsprod\NDA208772\
Submission Date	August 29, 2016
Submission Type	NME (Priority)
Brand Name	ALUNBRIG
Generic Name	Brigatinib
Dosage Form and Strength	30 and 90 mg tablets
Route of Administration	Oral
Proposed Indication	Treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib
Applicant	ARIAD Pharmaceuticals, Inc.
Associated INDs	110,935
OCP Review Team	Ruby Leong, Pharm.D., Hong Zhao, Ph.D., Hongshan Li, Ph.D., Jiang Liu, Ph.D.
OCP Final Signatory	NAM Atiqur Rahman, Ph.D. (Division Director)

The Office of Clinical Pharmacology (OCP) review is complete and has been added to the Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for details. The proposed brigatinib dosing regimen of 90 mg orally once daily for the first seven days, then 180 mg once daily, with the dose reduction schema in the event of adverse reactions is supported by the dose-response and exposure-response relationships for efficacy and for safety. From a Clinical Pharmacology standpoint, the NDA is approvable provided that the Applicant and the FDA reach an agreement regarding the labeling language.

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/s/

RUBY LEONG
01/25/2017

HONGSHAN LI
01/25/2017

JIANG LIU
01/25/2017

HONG ZHAO
01/25/2017
I concur.

NAM ATIQUR RAHMAN
01/25/2017

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	208772	**SDN**	5
Applicant	Ariad Pharmaceuticals	**Submission Date**	08/29/2016
Generic Name	Brigatinib	**Brand Name**	Alunbrig
Drug Class	Anaplastic lymphoma kinase (ALK) inhibitor		
Indication	Anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib		
Dosage Regimen	Starting dose of 90 mg orally once daily (QD) for the first seven days, then 180 mg QD, without regards to food		
Dosage Form	30 and 90 mg tablets	**Route of Administration**	Oral
OCP Division	DCPV	**OND Division**	DOP2

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Ruby Leong, Pharm.D.	Hong Zhao, Ph.D.
Pharmacometrics	Hongshan Li, Ph.D.	Jiang Liu, Ph.D.
Genomics		

Review Classification	☐ Standard ☑ Priority ☐ Expedited		
Filing Date	10/28/2016	**74-Day Letter Date**	11/11/2016
Review Due Date	1/29/2017	**PDUFA Goal Date**	4/29/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods 2 bioanalytical validation reports	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
☑ Metabolism Characterization	4	ARP213, ARP608, ARP609, ARP611
☑ Transporter Characterization	1	13ARIAP1R2
☑ Distribution	2	ARP210, 280N-1201

☑ Drug-Drug Interaction		2	ARP212, (b) (4) 123144
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☑ Relative Bioavailability		1	AP26113-15-106
☐ Bioequivalence			
☑ Food Effect		2	AP26113-13-103, AP26113-16-109
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose		Clinical pharmacology studies
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☑ Multiple Dose	2	AP26113-11-101, AP26113-13-201
☑ Mass Balance Study		1	AP26113-13-104
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☑ Race		1	AP26113-13-102; population pharmacokinetic (popPK) analyses
☑ Sex			PopPK analyses
☑ Geriatrics			PopPK analyses
☐ Pediatrics			Exempt from PREA due to orphan drug designation
☑ Hepatic Impairment			PopPK analyses
☑ Renal Impairment			PopPK analyses
☐ Genetics			
Extrinsic Factors			
☑ Effects on Primary Drug		1	AP26113-15-105
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☑ Patients			Exposure-response analyses
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☑ Patients			
☑ QT		1	AP26113-11-101
Pharmacometrics			
☑ Population Pharmacokinetics		1	ARIAD-BRI-02
☑ Exposure-Efficacy		2	ARP633, ARP636
☑ Exposure-Safety			

Total Number of Studies	**In Vitro**	11	**In Vivo**	12
Total Number of Studies to be Reviewed		11		12

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☑Yes ☐No ☐N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☑Yes ☐No ☐N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☑Yes ☐No ☐N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	Exempt from PREA due to orphan drug designation
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

The following Clinical pharmacology/Pharmacometrics information requests were conveyed to the Applicant:

1. Submit the analysis datasets and analysis programs (if applicable) associated with the following reports:
   a. "Population Pharmacokinetic Analysis of Brigatinib Based on Phase 1 and Phase 2 PK Data"
   b. "Analyses of the Relationship between Brigatinib Exposure and Selected Safety and Efficacy Outcomes"
   c. "Exposure Response Analyses of Brigatinib in the ALTA study (AP26113-13-201)"

2. With regards to the effect of organ dysfunction on brigatinib exposure:

   a. Update the population pharmacokinetic dataset with the classification of renal and hepatic function of patients:

      - Normal renal function, mild, moderate, or severe renal impairment based on CLcr and/or eGFR.

      - Normal hepatic function, mild, moderate, or severe hepatic impairment based on NCI criteria.

   b. Include available renal and hepatic function parameters such as SCr, CLcr calculated by the Cockcroft Gault equation and/or eGFR calculated by MDRD, AST/ALT, total bilirubin, etc. for each patient.

   c. Use boxplot to compare the population PK derived exposure (e.g., AUC, CL/F) between patients with normal renal function and patients with mild, moderate, or severe (if any) renal impairment with the sample size of each category listed below the box.

   d. Use boxplot to compare the population PK derived exposure (e.g., AUC, CL/F) between patients with normal hepatic function and patients with mild, moderate, or severe (if any) hepatic impairment (based on NCI criteria), with the sample size of each category listed below the box.

3. With regards to the dose recommendation for concomitant use of moderate CYP3A4 inducers:

   a. Provide a comparison of brigatinib exposure between patients with and without concomitant use of moderate CYP3A4 inducers (including dexamethasone) using data from Studies 101 and 201. Identify the patients with concomitant use of moderate CYP3A4 inducers and include information on the dose and duration of the moderate CYP3A4 inducer and time of administration with respect to brigatinib.

   b. Provide justification for your proposed labeling recommendation to avoid concomitant use of moderate CYP3A4 inducers supported by PBPK modeling and simulation.

   c. In the absence of PBPK analyses, propose a postmarketing study to assess the effect of moderate CYP3A4 inducers on brigatinib systemic exposure.

4. With regards to the dose recommendation for concomitant use of moderate CYP3A4 inhibitors:

   a. Provide a labeling recommendation for concomitant use of moderate CYP3A4 inhibitors supported by PBPK modeling and simulation.

   b. In the absence of PBPK analyses, propose a postmarketing study to assess the effect of moderate CYP3A4 inhibitors on brigatinib systemic exposure.

5. For Study 201, there are 13 subjects with brigatinib concentrations available based on "adpc.xpt" and “pc.xpt” datasets, but those subjects were excluded from NONMEM dataset "nm_pk_6aug2016.xpt" without explanation in the population PK report. Those 13 subjects are: 1001, 44001, 204001, 208007, 607006, 612005, 615001, 615006, 627001, 627003, 763003, 918012, and 995001. Please justify the exclusion of those subjects in the population PK analysis. Otherwise, update your population PK analysis dataset with those subjects included.

6. For Study 201, there are BID doses for subjects before Cycle 2 based on "adexd.xpt", but those BID doses are not reflected in the dosing records of "nm_pk_6aug2016.xpt". Please correct the dosing records of the population PK dataset so that the BID doses are correctly reflected.

7. For Subject 609008 of Study 201, WT is blank in the population PK dataset. Therefore, the analysis using NONMEM had set the subject’s body weight to 0 in estimating this subject’s individual V1 and CL. Please update the dataset by the subject’s actual body weight or update the NONMEM code by a reasonable imputation.

   Double check whether other mistakes exist in the population PK analysis for Study 201. Afterwards, check whether all similar mistakes exist in the other studies of the population PK dataset. Submit the updated dataset and population PK analysis.

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/s/

RUBY LEONG
10/24/2016

JEANNE FOURIE ZIRKELBACH
10/26/2016

STATISTICAL
FILING REVIEW

NDA/BLA #:	NDA 208772
Supplement #:	
Product Name:	Alunbrig® (brigatinib)
Indication(s):	Anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) in patients that have progressed on or are intolerant to crizotinib
Applicant:	ARIAD
Dates:	Received Date: August 29, 2016 April 29, 2017
Review Priority:	Priority
Statistical Reviewer:	Thomas Ly, PhD

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

Table 1: Summary of Trials to be Assessed in the Statistical Review

Trial ID	Design*	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
AP26113 -13-201	MC, R, PG 2 arms	Arm A/ N_A=112 90 mg once daily Arm B/ N_B=110 180 mg once daily with 7 day lead in at 90 mg once daily	Primary: Objective Response Rate (ORR) Key Secondary: Duration of Response	

MC: multi-center, R: randomized, PG: parallel group

Reference ID: 3994065

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	**Yes**
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	**Yes**
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	**NA**
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	**NA**
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	**Yes**

3. Electronic Data Assessment

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	\\CDSESUB1\evsprod\NDA208772\208772.enx
Were analysis datasets provided?	Yes
Dataset structure (e.g., SDTM or ADaM)	ADaM
Are the define files sufficiently detailed?	Yes
List the dataset(s) that contains the primary endpoint(s)	ADEFF, ADEFFW
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation? *	Yes
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	None
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	

* This might lead to the need for an information request or be a refuse to file issue depending on the ability to review the data.

Reference ID: 3994065

4. Filing Issues

Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	X			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)				
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	X			
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	X			
Application is free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements				

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE?
Yes

5. Comments to be Conveyed to the Applicant

None.

5.1. Refuse-to-File Issues

5.2. Information Requests/Review Issues

Reference ID: 3994065

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/s/

THOMAS T LY
10/03/2016

KUN HE
10/03/2016

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 208772 **Applicant: Ariad** **Stamp Date: 09-30-2016**

Drug Name: brigatinib (Alunbrig) **NDA/BLA Type: NME**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).	X			eCTD
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm	X			
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
8.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Text is contained in module 2.7.4
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Text is contained in module 2.7.3
10.	Has the applicant submitted a benefit-risk analysis for the product?	X			
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	X			505(b)(1)
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?			X	
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?			X	
14.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: AP26113-11-101 Study Title: A Phase 1/2 Study of the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-Tumor Activity of the Oral ALK/EGFR Inhibitor AP26113 Sample Size: 137 Treatment Arms: 66 in escalation (11 dose levels ranging from 30-300 mg once daily and 60-120 mg twice daily) and	X			

Reference ID: 3993247

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	71 in dose expansion Location in submission: module 5.3.5.2				
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: A Randomized Phase II Study of AP26113 in Patients with ALK-positive, Non-small Cell Lung Cancer (NSCLC) Previously Treated with Crizotinib Indication: Patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib	X			
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		The pivotal study was performed internationally, including in the U.S., and no preliminary reason exists to suggest that the study results will not be applicable to the US population.
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
21.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			ECG cardiac safety report was submitted as part of study AP26113-11-101.
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dosage (or dosage range) believed to be efficacious?			X	
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

Reference ID: 3993247

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	exposed as requested by the Division?				
25.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307 htm)?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	The pivotal study was performed internationally, including in the U.S., and no preliminary reason exists to suggest that the study results will not be applicable to the US population.
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

M.Naomi Horiba

Reviewing Medical Officer Date

Steven J. Lemery

Clinical Team Leader Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

Reference ID: 3993247

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/s/

MARGIT N HORIBA
09/30/2016

STEVEN J LEMERY
09/30/2016

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA

NDA Number: 208772 **Applicant:** ARIAD Pharmaceuticals Inc. **Stamp Date:** August 29, 2016

Drug Name: ALUNBRIG brigatinib) **NDA Type:** **505(b)(1)** new molecular entity (NME)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	√		CTD format
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	√		Electronic submission
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	√		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	√		Carcinogenicity – not done/not required Mutagenicity – done Teratogenicity –done Fertility – not done/not required Juvenile studies – not done/not required Acute and repeat dose toxicity – done (6-month in rats and monkeys) ADME – done Safety pharmacology – done (neurological, cardio, pulmonary)
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	√		Same formulation
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	√		Same route of administration
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	√		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	√		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	√		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	√		Sufficient for filing.
11	Has the applicant addressed any abuse potential issues in the submission?		√	Does not constitute a filing issue
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable. This NDA is NME

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? _YES__

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant. **N/A**

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. **None**

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/s/

M A GOHEER
09/26/2016

WHITNEY S HELMS
09/27/2016