Title: A Phase 3 Multicenter Open-label Study of Brigatinib (AP26113) versus Crizotinib in Patients with ALK-positive Advanced Lung Cancer

NCT Number: NCT02737501

Protocol Approve Date: 12 May 2020

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3 Multicenter Open-label Study of Brigatinib (AP26113) versus Crizotinib in Patients with ALK-positive Advanced Lung Cancer
Protocol Number:	AP26113-13-301
Study Phase:	Phase 3
Product Name:	Brigatinib
IND Reference Number:	IND 110,935
EudraCT Number:	2015-003447-19
Sponsor:	ARIAD Pharmaceuticals, Inc. a wholly owned subsidiary of Takeda Pharmaceutical Company Limited 40 Landsdowne Street Cambridge, MA 02139 USA Telephone: +1 (617) 679-7000
Protocol Issue Date:	12 May 2020
Version Number:	Version 4.0

PROTOCOL REVISION HISTORY:

Amendment Number	Protocol Version Number	Date
Original Protocol	Version 1.0	22 October 2015
Amendment 01	Version 2.0	21 September 2016
Amendment 02	Version 3.0	17 May 2018
Amendment 03	Version 4.0	12 May 2020

1.1 Protocol Amendment 03 Summary of Changes and Rationale

Protocol Amendment		
Summary of Changes Since the Last Version of the Approved Protocol		
Amendment Number 03 **Protocol Version Number 4.0**	**Amendment Date** **12 May 2020**	**Global**

Protocol Amendment Summary and Rationale:

This table describes the changes in reference to the protocol incorporating Amendment 02. The primary reasons for this amendment are to:

- update the "final statistical analysis" and "End-of Study" due to achievement of the primary efficacy endpoint at the pre-planned interim analysis. The study will close at approximately 3 years after the last patient was enrolled because the primary endpoint of blinded Independent Review Committee (BIRC) assessed progression-free survival (PFS) met the prespecified critical value at the first interim analysis and was confirmed at the second interim analysis.
- incorporate administrative changes resulting from the change of sponsor representatives.
- Provide clarification for some of the protocol language.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Description of Each Change and Rationale		**Sections Affected by Change**
Description	***Rationale***	***Location***
1. Updated Sponsor representatives and contact information	Administrative	Section 2 Signatory Page Section 3 Contact Information
2. Added the approximate duration of patient participation is 4 years	The study will close at approximately 3 years after the last patient was enrolled because the primary endpoint of blinded Independent Review Committee (BIRC) assessed progression-free survival (PFS) met the prespecified critical value at the first interim analysis and was confirmed at the second interim analysis.	Section 4 Protocol Synopsis Section 11.8.1 Approximate Duration of Patient Participation
3. Updated the approximate duration of the study to 4.5 years	See Item 3 above.	Section 4 Protocol Synopsis Section 11.8.2 Approximate Duration of Study
4. Added that the primary analysis of the primary endpoint will be performed at the End-of-Study if the study ended before 198 events PFS events were observed.	Added because the endpoint was met at the first interim analysis (before 198 events PFS events were observed) and was confirmed at the second interim analysis.	Section 4 Protocol Synopsis Section 15.5.2 Primary Efficacy Endpoint Analyses
5. Added that analysis of the final assessment of overall survival (OS) will also be performed at the end of the study.	Added because the primary endpoint was met at the first interim analysis and was confirmed at the second interim analysis.	Section 15.5.2 Primary Efficacy Endpoint Analyses
6. Added that patients may crossover in Arm B (crizotinib) to brigatinib with *"either"* BIRC "*or "investigator"* assessed progression.	For logistical purposes.	Section 11.1Study Procedure Description Section 13.1.2 Continuation of Treatment after Disease Progression
7. Added language for Acknowledgement of Receipt (AOR) when an SAE is submitted to Takeda or designee by facsimile.	Sponsor initiated a new process for SAE reporting for information sent via fax.	Section 14.2.2 Reporting Serious Adverse Events
8. Minor editorial revisions	Administrative	Throughout the protocol

2 SIGNATURE PAGES

2.1 Representatives from Sponsor

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible sponsor medical officer and other signatories can be found on the signature page.

Electronic Signatures may be found on the last page of this document.

PPD

2.2 Investigator Signature

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, including all statements regarding confidentiality. I will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the sponsor to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study drug and the study. I understand that the study may be terminated or enrollment suspended at any time by the sponsor, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with all applicable regulations.

Investigator's Signature	Date (dd-mmm-yyyy)

3 CONTACT INFORMATION

Sponsor	ARIAD Pharmaceuticals, Inc. a wholly owned subsidiary of Takeda Pharmaceutical Company Limited 40 Landsdowne Street Cambridge, MA 02139 USA Telephone: +1 (617) 679-7000
Sponsor Medical Monitor:	PPD

4 PROTOCOL SYNOPSIS

Sponsor	ARIAD Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceuticals International Co. 35 Landsdowne Street Cambridge, MA 02139-4234
Study Treatment	Brigatinib (AP26113)
Protocol Title	A Phase 3 Multicenter Open-label Study of Brigatinib (AP26113) versus Crizotinib in Patients with ALK-positive Advanced Lung Cancer
Development Phase	Phase 3
Summary and Study Rationale	Activating gene rearrangements in anaplastic lymphoma kinase (ALK) have been identified as driver mutations in approximately 2% to 7% of patients with non-small cell lung cancer (NSCLC) (Kwak et al, 2010; Wong et al, 2009). Crizotinib (XALKORI® USPI, Pfizer, Inc.) has demonstrated clinical efficacy in ALK+ NSCLC. Results from a phase 1 study and a phase 2 single-arm study of crizotinib demonstrated objective response rates (ORRs) of 61% and 50%, respectively (XALKORI® USPI, Pfizer, Inc.). These 2 studies served as the basis for accelerated approval of crizotinib for treatment of ALK+ advanced NSCLC in the United States (US) in 2011 and conditional marketing authorization in the European Union (EU) in 2012. The efficacy of crizotinib in ALK+ NSCLC patients has also been investigated in a randomized active-control study against chemotherapy (pemetrexed or docetaxel) (XALKORI® USPI, Pfizer, Inc.). A statistically significant improvement in progression-free survival (PFS) was observed in patients treated with crizotinib compared with patients treated with chemotherapy (hazard ratio, 0.49; 95% CI: 0.37 to 0.64; p<0.001). A median PFS of 7.7 months was seen with crizotinib versus 3.0 months with chemotherapy. Regular approval for crizotinib was granted by the US Food and Drug Administration (FDA), on the basis of this study, in 2013. In a separate randomized active-control study of crizotinib against pemetrexed-platinum doublet chemotherapy in patients with advanced previously untreated non-squamous ALK+ NSCLC, median PFS was 10.9 months in the crizotinib arm and 7.0 months in the chemotherapy arm (hazard ratio for progression or death with crizotinib, 0.45; 95% CI: 0.35 to 0.60; p<0.001) (Solomon et al, 2014). Currently, two tests are FDA-approved for detection of ALK+ NSCLC: the Vysis® ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit (Abbott Molecular, Inc.) and the Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems, Inc.), an immunohistochemistry (IHC) assay. Although crizotinib is an effective treatment for ALK+ NSCLC, almost half (39% and 52%, respectively) of ALK+ NSCLC patients in the two trials that supported its accelerated approval failed to achieve a response. For those patients who did respond, the benefit was relatively short with a median duration of response of 11 months (XALKORI® USPI, Pfizer, Inc.). In many patients, loss of response to crizotinib manifests as systemic progression, but in some patients the disease progresses only within the brain, possibly as a result of low central nervous system (CNS) penetration of crizotinib (Camidge et al, 2012; Costa et al, 2011). The underlying reason for failure to achieve a response to crizotinib (primary resistance) is difficult to identify, but suboptimal potency of the agent against the targeted oncogene could be a contributing factor. The mechanisms underlying loss of response (secondary or acquired resistance) to crizotinib are becoming more clear

(Camidge et al, 2012). Emerging data suggest that an important acquired resistance mechanism is the emergence of point mutations in the kinase domain of ALK (Katayama et al, 2012). Mutations that confer resistance to crizotinib (such as the gatekeeper mutant L1196M, as well as L1152R, G1269A, S1206Y, F1174L, D1203N, C1156Y, T1151Tins, and G1202R mutations) may act by reducing the binding affinity of crizotinib to ALK (Bang, 2012).

In some patients, loss of response to crizotinib may also have a pharmacologic basis, with inadequate drug exposure resulting from dose modifications, or changes in drug metabolism or transport over time. In all of these scenarios, a rational approach to overcoming resistance is the use of a more potent ALK inhibitor with a broader therapeutic window that suppresses the emergence of resistance mutations in ALK and that can also achieve deep and prolonged target inhibition both systemically and in the CNS (for patients with brain metastases).

Brigatinib is a novel, synthetic, orally-active ALK tyrosine kinase inhibitor (TKI) discovered and developed at ARIAD Pharmaceuticals, Inc. Brigatinib has demonstrated potent in-vitro inhibitory activity against activated ALK (approximately 10-fold more potent than crizotinib) and pan-inhibitory activity against all 17 ALK resistance mutants identified to date, including the L1196M gatekeeper mutation and the G1202R mutation.

The phase 1/2 clinical study of brigatinib (Study AP26113-11-101) consists of a phase 1 dose escalation portion in multiple tumor types, followed by a phase 2 expansion portion with defined clinical cohorts. Daily doses from 30 mg to 300 mg were investigated in 137 patients, including 79 ALK+ NSCLC patients, of which 71 (90%) had previously been treated with crizotinib. Three regimens were evaluated in phase 2: 90 mg QD, 90 mg QD for 7 days followed by escalation to 180 mg QD (90 mg QD→180 mg QD), and 180 mg QD.

As of 17 February 2015, the median time on treatment for all patients and ALK+ NSCLC patients was 7.4 months and 12.6 months, respectively. Median dose intensity for patients receiving the phase 2 doses explored in this study—90 mg QD (n=18), 90 mg QD→180 mg QD (n=32), and 180 mg QD (n=44)—was 90 mg/day, 177 mg/day, and 177 mg/day, respectively. For the 90 mg QD, 90 mg QD→180 mg QD, and 180 mg QD cohorts, 0%, 25%, and 14% of patients had dose reductions due to AEs and 17%, 25%, and 43% of patients had dose interruptions (≥3 days), respectively. A total of 13 patients (9.5%) discontinued treatment due to an AE.

The most commonly reported treatment emergent adverse events (TEAEs) in ≥15% of patients who received the 90 mg QD→180 mg QD (n=32) regimen were diarrhea (44%), fatigue (44%), nausea (41%), headache (28%), cough (28%), arthralgia (28%), amylase increased (25%), lipase increased (25%), constipation (22%), back pain (22%), hypertension (22%), aspartate aminotransferase increased (19%), decreased appetite (16%), alanine aminotransferase increased (16%), insomnia (16%), peripheral sensory neuropathy (16%), and joint swelling (16%). Grade 3 or greater TEAEs reported in 2 or more patients (>5%) who received the 90 mg QD→180 mg QD (n=32) regimen included: increased lipase (9%), hypertension (9%), pericardial effusion malignant (9%), dyspnea (6%), and alanine aminotransferase increased (6%).

During dose escalation and initial phase 2 expansion, patients were observed to experience pulmonary AEs such as dyspnea, hypoxia, pneumonia, and pneumonitis within the first 7 days of treatment at starting doses of 180 mg QD and higher. Many of these early pulmonary AEs occurred within 24 to 48 hours after initiating treatment. Based on these safety observations, 2 additional regimens were tested in the phase 2 portion (90 mg QD and 90 mg QD→180 mg QD). In the study overall, there were 13/137 (9%) patients with these early onset pulmonary events within the first 7 days of treatment: 2/2 (100%) patients at 300 mg QD, 2/10 (20%) patients at

	240 mg QD, 6/44 (14%) patients at 180 mg QD, 1/11 (9%) patients at 120 mg QD, and 2/50 (4%) patients at starting at 90 mg QD (including 90 mg QD and 90 mg QD→180 mg QD). The addition of a 90 mg QD 7 day lead in to therapy with 180 mg QD appears to lessen the incidence of early onset pulmonary events. Of 32 patients started at 90 mg for 7 days and then escalated to 180 mg, none (0%) experienced these early onset pulmonary symptoms within the first 7 days at 90 mg or after escalation to 180 mg. In evaluable ALK+ NSCLC patients treated with prior crizotinib, a 71% (50/70) overall response rate (ORR) was observed, including 4 complete responses (CRs). The ORR for the cohort that received 90 mg QD→180 mg QD was 81% (22/27 evaluable). An ORR of 100% was observed for crizotinib naïve patients (8/8), including 3 CRs. Median PFS was 13.4 months for patients treated with prior crizotinib. Median PFS was not reached for the crizotinib-naive patients, with a median time on treatment of 62 weeks (max: 134 weeks, ongoing) and 6/8 patients ongoing without progression. To evaluate the potential for brigatinib anti tumor activity in the CNS, a blinded independent radiological review of intracranial response was performed in ALK+ NSCLC patients with intracranial CNS metastases at baseline. In patients with measurable metastases, 53% (8/15) had an intracranial response; in those with only nonmeasurable metastases, 35.5% (11/31) had an intracranial response. Among patients who had no prior brain radiotherapy (n=21), intracranial ORR was 5/9 (55.6%) for patients with measurable lesions and 7/12 (58.3%) for those with only nonmeasurable lesions. For patients with a follow up scan (n=46), median intracranial PFS was 15.6 months. Based on the findings of Study AP26113-11-101, a pivotal 2-arm, open-label, phase 2 study of brigatinib in ALK+ NSCLC patients whose disease has progressed on therapy with crizotinib was designed (AP26113-13-201, "ALTA"). This study randomizes patients in a 1:1 fashion to one of two brigatinib regimen: 90 mg QD and 90 mg QD→180 mg QD. The study is currently enrolling patients with a target accrual of 218 patients. In summary, brigatinib was generally tolerated and has an acceptable safety profile for the stage of development up to regimens including 90 mg→180 mg QD. Brigatinib exhibited substantial anticancer activity in patients with ALK+ NSCLC, including patients who were crizotinib-naïve. Brigatinib is active in ALK+ brain metastases with frequent responses of clinically meaningful duration. There is strong rationale to evaluate brigatinib in the treatment of TKI-naïve ALK+ NSCLC.
Study Design	This is a phase 3, randomized, open-label, comparative, multicenter, international study in which ALK+ NSCLC patients who have not previously received an ALK-targeted TKI will be randomized in a 1:1 fashion to receive brigatinib (Arm A) or crizotinib (Arm B). Patients will be stratified by the presence of intracranial CNS metastases at baseline (Yes versus No) and prior chemotherapy use for locally advanced or metastatic disease (Yes versus No). For the purposes of stratification, prior chemotherapy is defined as completion of ≥1 full cycle of chemotherapy in the locally advanced or metastatic setting. Patients will be treated until they experience progressive disease (PD) assessed by the blinded Independent Review Committee (BIRC), intolerable toxicity, or another discontinuation criterion is met. Continuation of brigatinib beyond progression is permitted, at the investigator's discretion, if there is evidence of continued clinical benefit. Crossover in Arm B (crizotinib) to brigatinib is also permitted, at the investigator's discretion with the sponsor's medical monitor approval, for patients who have experienced objective progression assessed by the BIRC.

Study Objectives	The primary objective of the study is to compare the efficacy of brigatinib to that of crizotinib in ALK+ locally advanced or metastatic NSCLC patients naive to ALK inhibitors, as evidenced by PFS. The secondary objectives of the study are: 1. To compare the efficacy of brigatinib to that of crizotinib, as evidenced by confirmed ORR, time to/duration of response, disease control rate (DCR), and Overall Survival (OS) 2. To compare the efficacy in the CNS of brigatinib to that of crizotinib, as evidenced by intracranial response and intracranial PFS in those patients with intracranial CNS metastases at baseline 3. To assess the safety and tolerability of brigatinib in comparison with crizotinib 4. To determine pharmacokinetic (PK) parameters of brigatinib through population PK modeling 5. To assess patient-reported symptoms and health-related quality of life (HRQoL) with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 (v3.0) and its lung cancer module, QLQ-LC13 (v3.0) in patients treated with brigatinib compared to those treated with crizotinib CCI [redacted]

Study Endpoints	**Primary Endpoint:** PFS, as assessed by the BIRC, per RECIST v1.1 (Eisenhauer et al, 2009) **Secondary Endpoints:** 1. Confirmed ORR, as assessed by the BIRC, per RECIST v1.1 2. Confirmed intracranial ORR as assessed by the BIRC 3. Intracranial PFS, as assessed by the BIRC 4. OS 5. Duration of response, as assessed by the BIRC 6. Time to response, as assessed by the BIRC 7. Disease control rate, as assessed by the BIRC 8. Safety and tolerability 9. Change from baseline scores in global health status/quality of life (QOL) assessed with the EORTC QLQ-C30 (v3.0), and time-to-deterioration in dyspnea assessed with the EORTC QLQ-LC13 (v3.0) CCI [redacted]
Inclusion Criteria	All patients must meet all of the following eligibility criteria for study entry: 1. Have histologically or cytologically confirmed stage IIIB (locally advanced or recurrent and not a candidate for definitive multimodality therapy) or stage IV NSCLC. 2. Must meet one of the following two criteria: a. Have documentation of ALK rearrangement by a positive result from the Vysis® ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit or the Ventana ALK (D5F3) CDx Assay. The test must have been performed according to the product's instructions for use (IFU). b. Have documented ALK rearrangement by a different test and adequate tissue available for central laboratory testing by an FDA-approved test. Confirmation of central test positivity is not required prior to randomization. 3. Have sufficient tumor tissue available for central analysis (see the Study Reference Manual for minimum requirements) 4. Have at least 1 measurable (i.e., target) lesion per RECIST v1.1 (see Appendix C). 5. Recovered from toxicities related to prior anticancer therapy to NCI CTCAE v 4.0 grade ≤1. Note: treatment-related alopecia or peripheral neuropathy that are grade >1 are allowed if deemed irreversible.

	6. Are a male or female patient ≥18 years old. 7. Have adequate organ function, as determined by: a. ALT/AST ≤2.5 × upper limit of normal (ULN); ≤5 × ULN is acceptable if liver metastases are present b. Total serum bilirubin ≤1.5 × ULN (<3.0×ULN for patients with Gilbert syndrome) c. Serum creatinine ≤1.5 × ULN d. Serum lipase/amylase ≤1.5 × ULN e. Absolute neutrophil count (ANC) ≥1.5 × 10^9/L f. Platelet count ≥75 × 10^9/L g. Hemoglobin ≥10 g/dL 8. Have Eastern Cooperative Oncology Group (ECOG) performance status ≤2 (see Appendix B). 9. Have normal QT interval on screening ECG evaluation, defined as QT interval corrected (Fridericia) (QTcF) of ≤450 milliseconds (msec) in males or ≤470 msec in females. 10. For female patients of childbearing potential, have a negative pregnancy test documented prior to randomization. 11. For female and male patients who are fertile, agree to use a highly effective form of contraception with their sexual partners during the dosing period and for a period of at least 4 months after the end of treatment with brigatinib and at least 3 months after the end of treatment with crizotinib (Section 14.3.1). 12. Provide signed and dated informed consent indicating that the patient has been informed of all pertinent aspects of the study, including the potential risks, and is willingly participating. 13. Have the willingness and ability to comply with scheduled visit and study procedures.
Exclusion Criteria	Patients meeting any of the criteria below are ineligible for the study: 1. Previously received an investigational antineoplastic agent for NSCLC. 2. Previously received any prior TKI, including ALK-targeted TKIs. 3. Previously received more than 1 regimen of systemic anticancer therapy for locally advanced or metastatic disease. Note: a systemic anticancer therapy regimen will be counted if it is administered over at least 1 cycle. A new antineoplastic agent used as maintenance therapy will be counted as a new regimen. Neo-adjuvant or adjuvant systemic anticancer therapy will be counted as a prior regimen if completion of (neo) adjuvant therapy occurred <12 months prior to randomization. 4. Received chemotherapy or radiation within 14 days of first dose of study drug, except stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT). 5. Received anti-neoplastic monoclonal antibodies within 30 days of the first dose of study drug.

	6. Had major surgery within 30 days of the first dose of study drug, minor surgical procedures such as catheter placement or minimally invasive biopsies are allowed. 7. Have been diagnosed with another primary malignancy other than NSCLC, except for adequately treated non-melanoma skin cancer or cervical cancer in situ; definitively treated non-metastatic prostate cancer; or patients with another primary malignancy who are definitively relapse-free with at least 3 years elapsed since the diagnosis of the other primary malignancy. 8. Have symptomatic CNS metastases (parenchymal or leptomeningeal) at screening or asymptomatic disease requiring an increasing dose of corticosteroids to control symptoms within 7 days prior to randomization. Note: If a patient has worsening neurological symptoms or signs due to CNS metastasis, the patient needs to complete local therapy and be neurologically stable (with no requirement for an increasing dose of corticosteroids or use of anticonvulsants) for 7 days prior to randomization. 9. Have current spinal cord compression (symptomatic or asymptomatic and detected by radiographic imaging). Patients with leptomeningeal disease and without cord compression are allowed. 10. Be pregnant, planning a pregnancy, or breastfeeding 11. Have significant, uncontrolled, or active cardiovascular disease, specifically including, but not restricted to: a. Myocardial infarction (MI) within 6 months prior to the first dose of study drug b. Unstable angina within 6 months prior to first dose of study drug c. Congestive heart failure (CHF) within 6 months prior to first dose of study drug d. History of clinically significant atrial arrhythmia (including clinically significant bradyarrhythmia), as determined by the treating physician e. Any history of ventricular arrhythmia f. Cerebrovascular accident or transient ischemic attack within 6 months prior to first dose of study drug 12. Have uncontrolled hypertension. Patients with hypertension should be under treatment on study entry to control blood pressure. 13. Have a history or the presence at baseline of pulmonary interstitial disease, drug-related pneumonitis, or radiation pneumonitis. 14. Have an ongoing or active infection, including, but not limited to, the requirement for intravenous (IV) antibiotics. 15. Have a known history of human immunodeficiency virus (HIV) infection. Testing is not required in the absence of history. 16. Have a known or suspected hypersensitivity to brigatinib or its excipients. 17. Have a known or suspected hypersensitivity to crizotinib or its excipients. 18. Have malabsorption syndrome or other gastrointestinal (GI) illness or condition that could affect oral absorption of the study drug. 19. Have any condition or illness that, in the opinion of the investigator, would

	compromise patient safety or interfere with the evaluation of the study drug.
Approximate Number of Patients	Approximately 270 patients total (135 in Arm A, 135 in Arm B)
Approximate Duration of Patient Participation	Patients will continue to be treated with brigatinib (Arm A) or crizotinib (Arm B) until they experience disease progression assessed by the BIRC or intolerable toxicity. Treatment with brigatinib may be continued after progression, at the discretion of the investigator, if there is still evidence of clinical benefit. At the discretion of the investigator with the sponsor's medical monitor approval, patients who experience disease progression assessed by the BIRC while on crizotinib therapy may crossover to treatment with brigatinib. All patients who crossover to brigatinib from crizotinib must have a washout period of at least 10 days between treatments. On average, a patient is expected to participate in this study for approximately 4 years.
Approximate Duration of Study	The total estimated duration of the study is approximately 4.5 years, including 1.5 years to accrue patients, with at least 3 years for treatment and follow-up of the last patient. Since the study met the statistical significance at the first interim analysis and the primary endpoint was consistent at the second interim analysis, the study will be closed approximately 3 years after the last patient enrolled.
Approximate Number of Study Centers	Approximately 150 centers
Study Drug Administration and Modification	Patients will be randomized to receive brigatinib or crizotinib in a 1:1 fashion. Patients will be stratified by the presence of intracranial CNS metastases at baseline (Yes versus No) and prior chemotherapy use for locally advanced or metastatic disease (Yes versus No). For the purposes of stratification, prior chemotherapy is defined as completion of ≥1 full cycle of chemotherapy in the locally advanced or metastatic setting. **Arm A (brigatinib):** Brigatinib will be administered orally at a dose of 90 mg QD for 7 days, then 180 mg QD, continuously, with or without food. Patients will take the prescribed dose with water (recommended 240 mL). **Arm B (crizotinib):** Crizotinib will be administered as 250 mg orally BID, with or without food. Patients will take the prescribed dose with water (recommended 240 mL). **Dose Modifications** Dose interruptions or reductions should be implemented for patients who experience treatment-related AEs, based on the clinical judgment of the investigator. Criteria for dose modifications of brigatinib for drug-related toxicity are described in the protocol. The European Medicines Agency (EMA) Summary of Product Characteristics (SmPC) for crizotinib (XALKORI® SmPC, Pfizer, Inc.) will be used as a guideline for dose modification of patients in the crizotinib arm and is detailed in the protocol.
Concomitant Treatment	Palliative therapy and supportive care are permitted during the study for management of symptoms and underlying medical conditions that may develop during the study. Patients with CNS lesions requiring local radiotherapy such as SRS are allowed to continue brigatinib after appropriate interruption, as determined by the investigator with sponsor agreement; however, for analysis purposes, these patients will be considered to have progressive disease (PD).

	The following concurrent medications or procedures are prohibited for the duration of the study: 1. Any other systemic anticancer therapy, including, but not limited to: chemotherapeutic agents, immunotherapy, biological response modifiers (excluding growth factors), radiotherapy, and/or systemic hormonal therapy (with the exception of local therapies, such as SRS, used for palliative or symptomatic control of existing lesions, with appropriate treatment interruption at the discretion of the investigator). Use of any other investigational drug or device; 2. Medications that are known to be associated with the development of Torsades de Pointes (see Appendix E). Medications that prolong the QT interval, but are not known to be associated with Torsades de Pointes, should be avoided but are not prohibited; 3. Extensive surgery requiring inpatient care (patients may have an interruption in therapy for 14 days should emergency surgery be required). *Brigatinib* In vitro studies with human liver microsomes indicate that cytochrome P450 (CYP) 2C8 and CYP3A4 are involved in the human metabolism of brigatinib. Medications and dietary (grapefruit-containing products) or herbal products (St John's Wort) that are strong inhibitors or inducers of CYPs, in particular CYP2C8 or CYP3A4, should be avoided (see Appendix D). Brigatinib is not a reversible inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5, with IC_{50} values of >70 µM. Brigatinib is also not a metabolism-dependent or a time-dependent inhibitor of the CYPs tested. Hence, drug-drug interactions (DDIs) due to inhibition of CYPs by brigatinib are unlikely. *Crizotinib* Crizotinib is predominantly metabolized by CYP3A4/5. Coadministration of crizotinib with strong CYP3A inhibitors increases crizotinib plasma concentrations. Avoid concomitant use of strong CYP3A inhibitors, including, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, and voriconazole. Avoid grapefruit or grapefruit juice which may also increase plasma concentrations of crizotinib. Exercise caution with concomitant use of moderate CYP3A inhibitors. Crizotinib inhibits CYP3A both in vitro and in vivo. Coadministration of crizotinib with strong CYP3A inducers decreases crizotinib plasma concentrations. Avoid concomitant use of strong CYP3A inducers, including, but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's Wort. Avoid concomitant use of CYP3A substrates with narrow therapeutic range, including, but not limited, to alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus in patients taking crizotinib. If concomitant use of these CYP3A substrates with narrow therapeutic range is required in patients taking crizotinib, dose reductions of the CYP3A substrates may be required due to adverse reactions.
Efficacy Evaluation	Tumor response assessments will be performed every 8 weeks and evaluated per RECIST v1.1 by the BIRC and the investigator until BIRC-assessed disease progression. Tumor response (CR or partial response [PR]) should be confirmed ≥4 weeks after initial response. For patients in Arm A who continue brigatinib beyond disease progression, tumor assessments will continue to be performed every 8 weeks. Crossover in Arm B (crizotinib) to brigatinib treatment (Crossover Phase) is

	permitted, at the investigator's discretion, for patients who have experienced objective progression assessed by the BIRC. For these patients, the tumor response assessment with BIRC-assessed progression will be re-evaluated per RECIST v1.1 criteria as a new baseline for the Crossover Phase. Tumor response assessments will be performed every 8 weeks and evaluated per RECIST v1.1 by the BIRC and the investigator until BIRC-assessed disease progression. OS will be followed for approximately 3 years after the last patient has been randomized.
Safety Evaluation	Safety assessments will include physical and laboratory examinations, vital signs, and electrocardiograms (ECGs). Adverse events (AEs) will be graded according to the NCI CTCAE v4.0.
Pharmacokinetic Evaluations	Sparse plasma brigatinib concentration data obtained from this study will be included in integrated population PK analyses, along with data from study AP26113-11-101 and study AP26113-13-201, with the objective of further characterizing the plasma PK of brigatinib in the intended patient population, and to assess exposure-response (for efficacy) and exposure-safety relationships in patients receiving brigatinib.
Exploratory Biomarker Evaluations in Tissue and Blood	CCI [redacted]
Patient-Reported Symptoms and Quality of Life Assessments	Patient-reported symptoms and HRQoL will be collected by administering the EORTC QLQ-C30 (v3.0) and EORTC QLQ-LC13 (v3.0) questionnaires, which have been studied extensively, are validated, and are suitable for use in global clinical studies. The questionnaires will be administered to patients in their local language.
Statistical Methods	The primary analysis of the primary endpoint will be performed using a 2-sided stratified log-rank test (stratification factors: presence of intracranial CNS metastases at baseline [yes versus no], and prior chemotherapy use for locally advanced or metastatic disease [yes versus no]) to compare the BIRC-assessed PFS of patients randomized to brigatinib with the BIRC-assessed PFS of patients randomized to crizotinib. The overall (2-sided) Type I error rate will be controlled at 0.05. The primary analysis will be based on the intent-to-treat (ITT) population. PFS will be estimated for each treatment arm using the Kaplan-Meier method (Kaplan and Meier, 1958). Additionally, hazard ratios will be estimated using the Cox regression model with the stratification factors as covariates. Two interim analyses are planned after approximately 50% and 75% of the total expected events (progression or death) have been observed. An O'Brien-Fleming Lan-DeMets (DeMets and Lan, 1994) alpha spending function will be used to control the overall alpha level at 0.05 2-sided. The first interim analysis will be performed after the first 99 events have been observed. The primary endpoint of PFS will be tested at a 2-sided alpha level of 0.0042. A second interim analysis will be performed after 149 events and the primary endpoint will be tested at a 2-sided alpha level of 0.0194. The primary analysis of the primary endpoint will be performed after 198 events have been observed or at End-of-Study, whichever comes first, and will be tested at a 2-sided alpha level of 0.043. If

	the efficacy boundary is surpassed at an interim analysis, patients will remain on assigned treatments unless a survival advantage is noted. Further details of statistical analyses including the data handling rules will be provided in the Statistical Analysis Plan (SAP).
Rationale for Number of Patients	For the purposes of this sample size calculation, the median PFS for crizotinib is estimated as 10 months. Approximately 270 patients will be randomized in a 1:1 fashion to receive brigatinib or crizotinib. A total of 198 events (progression or death among the randomized patients) will provide 90% power to detect a 6-month improvement in PFS (hazard ratio=0.625). This power projection is based on a 2-sided log-rank test and is controlled at the 2-sided 0.043 level, adjusting for the proposed interim analysis plan. The number of events is fixed, but the enrollment number may change based on an assessment of the overall event rate pooled across treatment groups (prior to the close of enrollment).

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LIST OF APPENDICES

LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ARIAD	ARIAD Pharmaceuticals, Inc.
AST	aspartate aminotransferase
BAL	bronchoalveolar lavage
BID	twice daily
BIRC	blinded Independent Review Committee
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CK	creatine kinase
CNS	central nervous system
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events (version 4.0)
CYP	cytochrome P450
DCR	disease control rate
DDI	drug-drug interaction
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EEA	European Economic Area
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EML4	echinoderm microtubule-associated protein-like 4
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
FDA	Food and Drug Administration (United States)
FFPE	formalin-fixed, paraffin-embedded
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
GI	gastrointestinal
HIV	human immunodeficiency virus
HRQoL	health-related quality-of-life
IC_{50}	50% maximum inhibitory concentration
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors

Abbreviation	Term
IEC	Independent Ethics Committee
IFU	instructions for use
IGF-1R	insulin-like growth factor 1 receptor
IHC	immunohistochemistry
IRB	Institutional Review Board
IRC	independent review committee
ITT	intent-to-treat
IV	intravenous
KM	Kaplan-Meier
LD	longest diameter
LD_{50}	oral lethal dose
LDH	lactate dehydrogenase
LLT	lowest level term
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labor, and Welfare (Japan)
MI	myocardial infarction
MRI	magnetic resonance imaging
msec	millisecond
NCI	National Cancer Institute (of the United States)
NE	non-evaluable
NSCLC	non-small cell lung cancer
OCT	optical coherence tomography
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PR	partial response
PRO	patient-reported outcome
QD	once-daily
QLQ	Quality of Life Questionnaire
QOL	quality of life
QT	QT interval; a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc	heart rate-corrected QT interval (calculated)
QTcF	QT interval corrected (Fridericia)
RECIST	Response Evaluation Criteria in Solid Tumors (version 1.1)
SAE	serious adverse event
SAP	statistical analysis plan
SBRT	stereotactic body radiation therapy
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase

Abbreviation	Term
SLD	sum of longest diameter
SmPC	Summary of Product Characteristics (EMA)
SOC	System Organ Class
SRS	stereotactic radiosurgery
SUSAR	suspected unexpected and serious adverse reaction
TEAE	treatment emergent adverse event
TKI	tyrosine kinase inhibitor
TRAE	treatment-related adverse event
UE	unable to evaluate
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
WBRT	whole brain radiation therapy
β-HCG	beta-human chorionic gonadotropin

6 DEFINITIONS OF TERMS

Term	Definition
30 Days After Last Dose	At *30 days after last dose* of study drug, a patient completes all post-treatment discontinuation assessments.
Clinically Significant	A clinical observation or laboratory result that leads to a new intervention or change in therapy is defined in the context of this study as *clinically significant*.
Cycle	For the purposes of this study, a *cycle* consists of 28 days and is equivalent to a month in the measurement of study endpoints.
End-of-Treatment	The *end-of-treatment* occurs at the last dose of study drug or when the investigator and patient decide that the patient will receive no further study drug, whichever occurs later**.**
End-of-Study	*End-of-study* (completion) date is when all patients have completed all study visits or have otherwise discontinued from the study.
Enrolled Patient	An *enrolled patient* is a patient who has signed the informed consent form, completed all screening evaluations, and has been randomized to a treatment group.
Ethics Committee	Throughout this document, the term *Ethics Committee* (EC) refers to all appropriate properly constituted committees or boards recognized by the appropriate regulatory agencies for approving clinical studies. These include independent EC and Institutional Review Boards.
Evaluable for Efficacy	Any eligible patient who receives study drug is considered *evaluable for efficacy* analyses.
Evaluable for Safety	Any patient who receives study drug is considered *evaluable for safety* analyses.
Follow-up Period	The *follow-up period* for survival begins at the end of treatment and continues until patient contact discontinues.
Institutional Review Board	Throughout this document, the term *Institutional Review Board* (IRB) refers to all appropriate properly constituted committees or boards recognized by the appropriate regulatory agencies for approving clinical studies. These include independent ECs and IRBs.
Patient	Throughout this document, the term *patient* refers to a patient in this clinical research study.
QTcF	QT corrected (Fridericia) Calculation Formula: $QTcF=QT/(RR)^{1/3}$, where RR=the interval from the onset of one QRS complex to the onset of the next QRS complex, measured in seconds.

Term	Definition
Regulation	Throughout this document, the term *regulation* refers to all appropriate regulations, laws, and guidelines. This study will be conducted according to all appropriate regulations. The regulations may be international, national, or local and may include but not be limited to the Code of Federal Regulations (United States); Ministry of Health, Labor, and Welfare (MHLW): Ethical Guidelines for Clinical Research (Japan); MHLW: Good Clinical Practice Guidelines (Japan); Japan Pharmaceuticals Affairs Law; the International Conference on Harmonisation Guideline for Good Clinical Practice; and the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Patients.
Regulatory Agency	Throughout this document, the term *regulatory agency* refers to all applicable health and regulatory agencies. These may be international, national, or local and may include but not be limited to MHLW (Japan), Pharmaceuticals and Medical Devices Agency (PMDA), European Medicines Agency (EMA), and the United States Food and Drug Administration (FDA).
Screening Period	The *screening period* for a patient begins when the informed consent form is signed and continues until randomization has taken place.
Sponsor	Throughout this document, the term *sponsor* refers to all applicable departments within ARIAD Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceuticals or its designee.
Study Reference Manual	In the context of this study, *Study Reference Manual* is a general term for the information provided to sites on technical aspects of the study.
Study Drug	For the purposes of this protocol, *study drug* refers to brigatinib and crizotinib.
Study Start Date	The *study start date* is the date that the first patient signs the informed consent form.
Suspected Adverse Reaction	A *suspected adverse reaction* is any adverse event (defined in Section 14.1.1) for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of regulatory reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.
Treatment Period	The *treatment period* is from time of first dose until 30 days past last dose.

7 INTRODUCTION

7.1 Background

Activating gene rearrangements in anaplastic lymphoma kinase (ALK) have been identified as driver mutations in approximately 2% to 7% of patients with non-small cell lung cancer (NSCLC) (Kwak et al, 2010; Wong et al, 2009). Crizotinib (XALKORI® USPI, Pfizer, Inc.) has demonstrated clinical efficacy in ALK+ NSCLC. Results from a phase 1 study and a phase 2 single-arm study of crizotinib demonstrated objective response rates (ORRs) of 61% and 50%, respectively (XALKORI® USPI, Pfizer, Inc.). These 2 studies served as the basis for accelerated approval of crizotinib for treatment of ALK+ advanced NSCLC in the United States (US) in 2011 and conditional marketing authorization in the European Union (EU) in 2012. The efficacy of crizotinib in ALK+ NSCLC patients has also been investigated in a randomized active-control study against chemotherapy (pemetrexed or docetaxel) (XALKORI® USPI, Pfizer, Inc.). A statistically significant improvement in progression-free survival (PFS) was observed in patients treated with crizotinib compared with patients treated with chemotherapy (hazard ratio, 0.49; 95% CI: 0.37 to 0.64; p<0.001). A median PFS of 7.7 months was seen with crizotinib versus 3.0 months with chemotherapy. Regular approval for crizotinib was granted by the US Food and Drug Administration (FDA), on the basis of this study, in 2013. In a separate randomized active-control study of crizotinib against pemetrexed-platinum doublet chemotherapy in patients with advanced previously untreated non-squamous ALK+ NSCLC, median PFS was 10.9 months in the crizotinib arm and 7.0 months in the chemotherapy arm (hazard ratio for progression or death with crizotinib, 0.45; 95% CI: 0.35 to 0.60; p<0.001) (Solomon et al, 2014). Currently, two tests are FDA-approved for detection of ALK+ NSCLC: the Vysis® ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit (Abbott Molecular, Inc.) and the Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems, Inc.), an immunohistochemistry (IHC) assay.

Although crizotinib is an effective treatment for ALK+ NSCLC, almost half (39% and 52%, respectively) of ALK+ NSCLC patients in the two trials that supported its accelerated approval failed to achieve a response. For those patients who did respond, the benefit was relatively short with a median duration of response of 11 months (XALKORI® USPI, Pfizer, Inc.). In many patients, loss of response to crizotinib manifests as systemic progression, but in some patients the disease progresses only within the brain, possibly as a result of low central nervous system (CNS) penetration of crizotinib (Camidge et al, 2012; Costa et al, 2011).

The underlying reason for failure to achieve a response to crizotinib (primary resistance) is difficult to identify, but suboptimal potency of the agent against the targeted oncogene could be a contributing factor. The mechanisms underlying loss of response (secondary or acquired resistance) to crizotinib are becoming more clear (Camidge et al, 2012). Emerging data suggest that an important acquired resistance mechanism is the emergence of point mutations in the kinase domain of ALK (Katayama et al, 2012). Mutations that confer resistance to crizotinib (such as the gatekeeper mutant L1196M, as well as L1152R, G1269A, S1206Y, F1174L, D1203N, C1156Y, T1151Tins, and G1202R mutations) may act by reducing the binding affinity of crizotinib to ALK (Bang, 2012).

In some patients, loss of response to crizotinib may also have a pharmacologic basis, with inadequate drug exposure resulting from dose modifications, or changes in drug metabolism or

transport over time. In all of these scenarios, a rational approach to overcoming resistance is the use of a more potent ALK inhibitor with a broader therapeutic window that suppresses the emergence of resistance mutations in ALK and that can also achieve deep and prolonged target inhibition both systemically and in the CNS (for patients with brain metastases).

7.2 Nonclinical Summary

7.2.1 Nonclinical Activity Against ALK

Brigatinib is a novel, synthetic, orally-active ALK tyrosine kinase inhibitor (TKI) discovered and developed at ARIAD Pharmaceuticals, Inc. In nonclinical studies, brigatinib has been shown to:

- Inhibit growth of ALK+ human tumor-derived cell lines with potency and selectivity approximately 10-fold greater than that of crizotinib
- Potently inhibit all 17 ALK secondary mutations identified to date that confer resistance to crizotinib or the second generation ALK inhibitors, ceritinib, and alectinib. Mean brigatinib concentrations in patients dosed at 90 or 180 mg daily, corrected for the functional effects of protein binding, were found to exceed the IC_{50} values for native echinoderm microtubule-associated protein-like 4 (EML4)-ALK and 16 resistance mutants by at least 2-fold. The only exception was the G1202R mutant, whose IC_{50} was substantially exceeded by brigatinib levels achieved at 180 mg but not 90 mg daily dosing.
- Suppress the emergence of any resistant ALK mutant in an in vitro mutagenesis assay, at concentrations that can be achieved clinically
- Induce regressions or inhibit growth of tumor xenografts driven by native ALK or mutant variants that confer clinical resistance
- Prolong survival of mice in an ALK-dependent orthotopic brain tumor model

Refer to the Investigator's Brochure for a more comprehensive presentation of the nonclinical data.

7.2.2 Nonclinical Activity Against Other Targets

In vitro kinase assays have revealed that brigatinib has potent inhibitory activity against kinases including activated epidermal growth factor receptor (EGFR) mutants commonly observed in NSCLC (e.g. exon 19 deletion, L858R, and activated EGFR mutants containing the T790M gatekeeper mutation), ROS1, CHK2, and insulin-like growth factor 1 receptor (IGF-1R).

7.3 Brigatinib Clinical Summary

Two company-sponsored clinical studies with brigatinib are being conducted in patients:

- A phase 1/2 study of the safety, tolerability, pharmacokinetics (PK) and preliminary antitumor activity of brigatinib in advanced malignancies, including ALK+ NSCLC (study AP26113-11-101)
- A pivotal phase 2 study in patients with advanced or metastatic ALK+ NSCLC whose disease has progressed on therapy with crizotinib (study AP26113-13-201; ALTA)

7.3.1 Phase 1/2 Trial: Study AP26113-11-101

The phase 1/2 clinical study of brigatinib (Study AP26113-11-101) consists of a phase 1 dose escalation portion in multiple tumor types, followed by a phase 2 expansion portion with defined clinical cohorts. Daily doses from 30 mg to 300 mg were investigated in 137 patients, including 79 ALK+ NSCLC patients, of which 71 (90%) had previously been treated with crizotinib. Three regimens were evaluated in phase 2: 90 mg QD, 90 mg QD for 7 days followed by escalation to 180 mg QD (90 mg QD→180 mg QD), and 180 mg QD.

As of 17 February 2015, the median time on treatment for all patients and ALK+ NSCLC patients was 7.4 months and 12.6 months, respectively. Median dose intensity for patients receiving the phase 2 doses explored in this study—90 mg QD (n=18), 90 mg QD→180 mg QD (n=32), and 180 mg QD (n=44)—was 90 mg/day, 177 mg/day, and 177 mg/day, respectively. For the 90 mg QD, 90 mg QD→180 mg QD, and 180 mg QD cohorts, 0%, 25%, and 14% of patients had dose reductions due to AEs and 17%, 25%, and 43% of patients had dose interruptions (≥3 days), respectively. A total of 13 patients (9.5%) discontinued treatment due to an AE.

The most commonly reported treatment-emergent adverse events (TEAEs) in ≥15% of patients who received the 90 mg QD→180 mg QD (n=32) regimen were diarrhea (44%), fatigue (44%), nausea (41%), headache (28%), cough (28%), arthralgia (28%), amylase increased (25%), lipase increased (25%), constipation (22%), back pain (22%), hypertension (22%), aspartate aminotransferase increased (19%), decreased appetite (16%), alanine aminotransferase increased (16%), insomnia (16%), peripheral sensory neuropathy (16%), and joint swelling (16%). Grade 3 or greater TEAEs reported in 2 or more patients (>5%) who received the 90 mg QD→180 mg QD (n=32) regimen included: increased lipase (9%), hypertension (9%), pericardial effusion malignant (9%), dyspnea (6%), and alanine aminotransferase increased (6%).

During dose escalation and initial phase 2 expansion, patients were observed to experience pulmonary AEs such as dyspnea, hypoxia, pneumonia, and pneumonitis within the first 7 days of treatment at starting doses of 180 mg QD and higher. Many of these early pulmonary AEs occurred within 24 to 48 hours after initiating treatment. Based on these safety observations, 2 additional regimens were tested in the phase 2 portion (90 mg QD and 90 mg QD→180 mg QD). In the study overall, there were 13/137 (9%) patients with these early onset pulmonary events within the first 7 days of treatment: 2/2 (100%) patients at 300 mg QD, 2/10 (20%) patients at 240 mg QD, 6/44 (14%) patients at 180 mg QD, 1/11 (9%) patients at 120 mg QD, and 2/50 (4%) patients at starting at 90 mg QD (including 90 mg QD and 90 mg QD→180 mg QD). The addition of a 90 mg QD 7-day lead-in to therapy with 180 mg QD appears to lessen the incidence of early onset pulmonary events. Of 32 patients started at 90 mg for 7 days and then escalated to 180 mg, none (0%) experienced these early onset pulmonary symptoms within the first 7 days at 90 mg or after escalation to 180 mg.

In evaluable ALK+ NSCLC patients treated with prior crizotinib, a 71% (50/70) overall response rate (ORR) was observed, including 4 complete responses (CRs). The ORR for the cohort that received 90 mg QD→180 mg QD was 81% (22/27 evaluable). An ORR of 100% was observed for crizotinib-naïve patients (8/8), including 3 CRs. Median PFS was 13.4 months for patients treated with prior crizotinib. Median PFS was not reached for the crizotinib-naive patients, with a median time on treatment of 62 weeks (max: 134 weeks, ongoing) and 6/8 patients ongoing without progression.

To evaluate the potential for brigatinib anti-tumor activity in the CNS, a blinded independent radiological review of intracranial response was performed in ALK+ NSCLC patients with intracranial CNS metastases at baseline. In patients with measurable metastases, 53% (8/15) had an intracranial response; in those with only nonmeasurable metastases, 35.5% (11/31) had an intracranial response. Among patients who had no prior brain radiotherapy (n=21), intracranial ORR was 5/9 (56%) for patients with measurable lesions and 7/12 (58.3%) for those with only nonmeasurable lesions. For patients with a follow-up scan (n=46), median intracranial PFS was 15.6 months.

7.3.2 Study AP26113-13-201 (ALTA)

A pivotal phase 2 study of patients with advanced or metastatic ALK+ NSCLC whose disease has progressed on therapy with crizotinib (Study AP26113-13-201; ALTA) is ongoing. This study randomizes patients in a 1: 1 fashion between 2 brigatinib treatment regimens: 90 mg QD (Arm A) and 90 mg QD→180 mg QD (Arm B). A total of 218 patients are planned to be enrolled.

As of 15 June 2015, 69 and 71 patients in Arm A and Arm B, respectively, were included an interim analysis of the safety population. Median duration of treatment was 89 days (range: 3 to 249 days) in Arm A and 88 days (range: 2 to 356 day) in Arm B. TEAEs occurring in ≥10% of patients in either arm are summarized in Table 1, with the most commonly reported events (≥15% overall) including diarrhea, cough, nausea, fatigue, dyspnea and headache. TEAEs ≥grade 3 in 2 or more patients are summarized in Table 2, with the most commonly reported grade 3 to grade 5 events (≥3% overall) including neoplasm progression, pneumonia and hypertension. Across both arms, 8/140 (5.7%) patients experienced a pulmonary SAE without a conclusive alternative etiology (e.g. tumor progression, infectious) with symptoms starting within the first 7 days of treatment at 90 mg QD (pneumonitis, n=4; pneumonia, n=3; atypical pneumonia; n=1). No events have been observed to date in Arm B upon escalation to 180 mg QD.

Table 1 Treatment Emergent Adverse Events (All Grades) Occurring in ≥10% of Patients in Study AP26113-13-201

Preferred Term	Patients With Adverse Events by Arm and Overall, n (%)		
	Arm A (90 mg), N=69	Arm B (90 mg →180mg), N=71	Total, N=140
Patients with at least 1 adverse event	61 (88.4)	59 (83.1)	120 (85.7)
Diarrhoea	13 (18.8)	15 (21.1)	28 (20.0)
Cough	12 (17.4)	15 (21.1)	27 (19.3)
Nausea	12 (17.4)	14 (19.7)	26 (18.6)
Fatigue	10 (14.5)	14 (19.7)	24 (17.1)
Dyspnoea	13 (18.8)	8 (11.3)	21 (15.0)
Headache	8 (11.6)	13 (18.3)	21 (15.0)
Vomiting	12 (17.4)	7 (9.9)	19 (13.6)
Amylase increased	5 (7.2)	9 (12.7)	14 (10.0)
Blood creatine phosphokinase increased	5 (7.2)	8 (11.3)	13 (9.3)
Decreased appetite	7 (10.1)	6 (8.5)	13 (9.3)
Hypertension	4 (5.8)	9 (12.7)	13 (9.3)
Pyrexia	9 (13.0)	2 (2.8)	11 (7.9)
Muscle spasms	1 (1.4)	8 (11.3)	9 (6.4)

Source: AP26113-13-201 Table 5.1, Table 5.2, Table 5.3. Data extraction date: 15 June 2015.

Note: Adverse events are coded using Medical Dictionary for Regulatory Activities (MedDRA 18.0).

Table 2 Treatment Emergent Adverse Events ≥ Grade 3 in 2 or More Patients in Study AP26113-13-201

Preferred Term	Patients With Adverse Events by Arm and Overall, n (%)					
	Arm A (90 mg), N=69		Arm B (90→180mg), N=71		Total, N=140	
	Grade 3-4	Grade 5	Grade 3-4	Grade 5	Grade 3-4	Grade 5
Patients with at least 1 adverse event	10 (14.5)	7 (10.1)	17 (23.9)	3 (4.2)	27 (19.3)	10 (7.1)
Neoplasm progression	0	4 (5.8)	0	2 (2.8)	0	5 (3.6)
Pneumonia	2 (2.9)	1 (1.4)	1 (1.4)	1 (1.4)	3 (2.1)	2 (1.4)
Hypertension	1 (1.4)	0	4 (5.6)	0	5 (3.6)	0
Dyspnoea	3 (4.3)	0	1 (1.4)	0	4 (2.9)	0
Blood creatine phosphokinase increased	1 (1.4)	0	3 (4.2)	0	4 (2.9)	0
Lipase increased	2 (2.9)	0	1 (1.4)	0	3 (2.1)	0
Rash	1 (1.4)	0	2 (2.8)	0	3 (2.1)	0
Rash pruritic	1 (1.4)	0	1 (1.4)	0	2 (1.4)	0
Pneumonitis	0	0	2 (2.8)	0	2 (1.4)	0

Source: AP26113-13-201 Table 5.1, Table 5.2, Table 5.3. Data extraction date: 15 June 2015.

Note: Adverse events are coded using Medical Dictionary for Regulatory Activities(MedDRA 18.0).

Refer to the Investigator's Brochure for a more comprehensive summary of the safety and efficacy data from brigatinib clinical studies.

7.4 Rationale for the Phase 3 Study of Brigatinib in ALK-inhibitor-naive ALK+ NSCLC

There continues to be a need to explore new treatment options for patients with ALK+ NSCLC who are naïve to treatment with an ALK-targeted TKI. Although crizotinib is an effective treatment for ALK+ NSCLC, almost half of ALK+ NSCLC patients in the pivotal trials that supported its accelerated approval failed to achieve a response. PFS was relatively short in the

2 randomized phase 3 trials, with a median duration of 7.7 to 10.9 months. Chemotherapy is also used although it is not specifically approved for use in ALK+ NSCLC patients, with median PFS duration of 7.0 months with first line platinum doublet chemotherapy. New therapies are needed to improve response rates, provide greater durability of response, and to overcome potential mechanisms of resistance to ALK-targeted therapy, including the emergence of secondary resistance mutations in ALK and progression in the CNS.

Based on the promising activity profile of brigatinib in vitro and in vivo and the clinical activity demonstrated in the phase 1/2 study (Study AP26113-11-101) and Phase 2 study (Study AP26113-13-201, ALTA), this phase 3 study will evaluate brigatinib in an ALK+ NSCLC patient population not previously treated with an ALK inhibitor.

7.5 Rationale for Proposed Phase 3 Dose

Brigatinib has an acceptable safety profile at starting doses of 90 mg QD (including dose escalation to 180 mg QD after 1 week). The 7-day run-in period at 90 mg QD prior to escalation to 180 mg QD reduced the frequency of pulmonary toxicity observed with a starting dose of 180 mg, and pulmonary toxicity has not been seen upon escalation to 180 mg. Taken together, the preliminary safety data from study AP26113-13-201 and longer follow up safety data in study AP26113-11-101 show that the AE profile of the 90 mg QD→180 mg QD is similar qualitatively and quantitatively to that of 90 mg QD. Mean plasma concentrations in patients dosed at 90 or 180 mg QD in study AP26113-11-101 were found to exceed the IC_{50} values for native EML4-ALK and all 17 resistance mutants tested by at least 2-fold, with the exception of the G1202R mutant, whose IC_{50} was substantially exceeded by brigatinib levels achieved at 180 mg QD but not 90 mg QD dosing. This suggests that the higher 180 mg QD dose may prevent the emergence of a broader array of ALK resistance mutations than 90 mg QD.

Importantly, with likely higher CNS exposure, the 180 mg QD dose may also provide increased activity against brain metastases. In order to optimize PFS and control CNS disease there is strong rationale to use the highest safe dose of brigatinib (90 mg QD for 7 days followed by 180 mg QD).

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study is to compare the efficacy of brigatinib to that of crizotinib in ALK+ locally advanced or metastatic NSCLC patients naive to ALK inhibitors, as evidenced by PFS.

8.2 Secondary Objectives

The secondary objectives of the study are:

1. To compare the efficacy of brigatinib to that of crizotinib, as evidenced by confirmed ORR, time to/duration of response, disease control rate (DCR), and Overall Survival (OS)

2. To compare the efficacy in the CNS of brigatinib to that of crizotinib, as evidenced by intracranial response and intracranial PFS in those patients with intracranial CNS metastases at baseline
3. To assess the safety and tolerability of brigatinib in comparison with crizotinib
4. To determine PK parameters of brigatinib through population PK modeling
5. To assess patient-reported symptoms and health-related quality of life (HRQoL) with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 (v3.0) and its lung cancer module, QLQ-LC13 (v3.0) in patients treated with brigatinib compared to those treated with crizotinib

8.3 Exploratory Objectives

CCI [redacted]

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a phase 3, randomized, open-label, comparative, multicenter, international study in which ALK+ NSCLC patients who have not previously received an ALK-targeted TKI will be randomized in a 1:1 fashion to receive brigatinib (Arm A) or crizotinib (Arm B).

Patients will be stratified by the presence of CNS metastases at baseline (Yes versus No) and prior chemotherapy used for locally advanced or metastatic disease (Yes versus No). For the purposes of stratification, prior chemotherapy is defined as completion of ≥1 full cycle of chemotherapy in the locally advanced or metastatic setting. An estimated 270 patients (135 in Arm A, 135 in Arm B) will be enrolled at approximately 150 centers.

Patients will be treated until they experience progressive disease (PD) assessed by the blinded Independent Review Committee (BIRC), intolerable toxicity, or another discontinuation criterion is met. Continuation of brigatinib beyond progression is permitted, at the investigator's discretion, if there is evidence of continued clinical benefit. Crossover from Arm B (crizotinib) to brigatinib is also permitted, at the investigator's discretion with the sponsor's medical monitor approval, for patients who have experienced objective progression assessed by the BIRC.

Throughout the study, AEs will be assessed and categorized by the US National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), v4.0 (see Appendix A). Patients will be evaluated according to the Schedule of Events in Section 11.1. Patients will be supplied study drug until they discontinue from the study.

9.1.1 Primary Endpoint

PFS, as assessed by the BIRC, per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Eisenhauer et al, 2009).

9.1.2 Secondary Endpoints

1. Confirmed ORR, as assessed by the BIRC, per RECIST v1.1
2. Confirmed intracranial ORR, as assessed by the BIRC
3. Intracranial PFS, as assessed by the BIRC
4. OS
5. Duration of response, as assessed by the BIRC
6. Time to response, as assessed by the BIRC
7. Disease control rate, as assessed by the BIRC
8. Safety and tolerability
9. Change from baseline scores in global health status/quality of life (QOL) assessed with the EORTC QLQ-C30 (v3.0), and time-to-deterioration in dyspnea assessed with the EORTC QLQ-LC13 (v3.0)

9.1.3 Exploratory Endpoints

CCI

[redacted]

9.2 Randomization

Patients will be randomized in a 1:1 ratio to receive either brigatinib 90 mg once daily (QD) orally for 7 days followed by 180 mg QD orally continuously (Arm A) or crizotinib 250 mg twice daily (BID) orally (Arm B). Patients will be stratified by the following 2 factors, each having 2 levels:

1. Intracranial CNS metastases at baseline (yes versus no)
2. Prior chemotherapy use for locally advanced or metastatic disease (yes versus no). For the purposes of stratification, prior chemotherapy is defined as completion of ≥1 full cycle of chemotherapy in the locally advanced or metastatic setting.

Specific instructions for randomization will be supplied in the Study Reference Manual. Randomization procedures should be performed following completion of eligibility assessments and prior to the initiation of treatment. This study is unblinded; patients, investigators, and the sponsor will know the identity of each patient's study drug.

10 SELECTION OF STUDY POPULATION

All patients must take part in the informed consent process. This process is described in Section 17.2. Screening tests and procedures used to establish eligibility are outlined in Section 11.1. Documentation from the screening period is required for each inclusion and exclusion criterion.

10.1 Inclusion Criteria

All patients must meet all of the following eligibility criteria for study entry:

1. Have histologically or cytologically confirmed stage IIIB (locally advanced or recurrent and not a candidate for definitive multimodality therapy) or stage IV NSCLC.
2. Must meet one of the following two criteria:
   a. Have documentation of ALK rearrangement by a positive result from the Vysis® ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit or the Ventana ALK (D5F3) CDx Assay. The test must have been performed according to the product's instructions for use (IFU).
   b. Have documented ALK rearrangement by a different test and adequate tissue available for central laboratory testing by an FDA-approved test. Confirmation of central test positivity is not required prior to randomization.
3. Have sufficient tumor tissue available for central analysis (see the Study Reference Manual for minimum requirements)
4. Have at least 1 measurable (i.e., target) lesion per RECIST v1.1 (see Appendix C).
5. Recovered from toxicities related to prior anticancer therapy to NCI CTCAE v 4.0 grade ≤1. Note: treatment-related alopecia or peripheral neuropathy that are grade >1 are allowed if deemed irreversible.
6. Are a male or female patient ≥18 years old.
7. Have adequate organ function, as determined by:
   a. ALT/AST ≤2.5 × upper limit of normal (ULN); ≤5 × ULN is acceptable if liver metastases are present
   b. Total serum bilirubin ≤1.5 × ULN (<3.0×ULN for patients with Gilbert syndrome)
   c. Serum creatinine ≤1.5 × ULN
   d. Serum lipase/amylase ≤1.5 × ULN
   e. Absolute neutrophil count (ANC) ≥1.5 × 10^9/L
   f. Platelet count ≥75 × 10^9/L
   g. Hemoglobin ≥10 g/dL
8. Have Eastern Cooperative Oncology Group (ECOG) performance status ≤2 (see Appendix B).

9. Have normal QT interval on screening ECG evaluation, defined as QT interval corrected (Fridericia) (QTcF) of ≤450 milliseconds (msec) in males or ≤470 msec in females.
10. For female patients of childbearing potential, have a negative pregnancy test documented prior to randomization.
11. For female and male patients who are fertile, agree to use a highly effective form of contraception with their sexual partners during the dosing period and for a period of at least 4 months after the end of treatment with brigatinib and at least 3 months after the end of treatment with crizotinib (Section 14.3.1).
12. Provide signed and dated informed consent indicating that the patient has been informed of all pertinent aspects of the study, including the potential risks, and is willingly participating.
13. Have the willingness and ability to comply with scheduled visit and study procedures.

10.2 Exclusion Criteria

Patients meeting any of the criteria below are ineligible for the study:

1. Previously received an investigational antineoplastic agent for NSCLC.
2. Previously received any prior TKI, including ALK-targeted TKIs.
3. Previously received more than 1 regimen of systemic anticancer therapy for locally advanced or metastatic disease.

   Note: a systemic anticancer therapy regimen will be counted if it is administered over at least 1 cycle. A new antineoplastic agent used as maintenance therapy will be counted as a new regimen. Neo-adjuvant or adjuvant systemic anticancer therapy will be counted as a prior regimen if completion of (neo) adjuvant therapy occurred <12 months prior to randomization.
4. Received chemotherapy or radiation within 14 days of first dose of study drug, except stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT).
5. Received anti-neoplastic monoclonal antibodies within 30 days of the first dose of study drug.
6. Had major surgery within 30 days of the first dose of study drug, minor surgical procedures such as catheter placement or minimally invasive biopsies are allowed.
7. Have been diagnosed with another primary malignancy other than NSCLC, except for adequately treated non-melanoma skin cancer or cervical cancer in situ; definitively treated non-metastatic prostate cancer; or patients with another primary malignancy who are definitively relapse-free with at least 3 years elapsed since the diagnosis of the other primary malignancy.
8. Have symptomatic CNS metastases (parenchymal or leptomeningeal) at screening or asymptomatic disease requiring an increasing dose of corticosteroids to control symptoms within 7 days prior to randomization.

Note: If a patient has worsening neurological symptoms or signs due to CNS metastasis, the patient needs to complete local therapy and be neurologically stable (with no requirement for an increasing dose of corticosteroids or use of anticonvulsants) for 7 days prior to randomization.

9. Have current spinal cord compression (symptomatic or asymptomatic and detected by radiographic imaging). Patients with leptomeningeal disease and without cord compression are allowed.
10. Be pregnant, planning a pregnancy, or breastfeeding
11. Have significant, uncontrolled, or active cardiovascular disease, specifically including, but not restricted to:
    a. Myocardial infarction (MI) within 6 months prior to the first dose of study drug
    b. Unstable angina within 6 months prior to first dose of study drug
    c. Congestive heart failure (CHF) within 6 months prior to first dose of study drug
    d. History of clinically significant atrial arrhythmia (including clinically significant bradyarrhythmia), as determined by the treating physician
    e. Any history of ventricular arrhythmia
    f. Cerebrovascular accident or transient ischemic attack within 6 months prior to first dose of study drug
12. Have uncontrolled hypertension. Patients with hypertension should be under treatment on study entry to control blood pressure.
13. Have a history or the presence at baseline of pulmonary interstitial disease, drug-related pneumonitis, or radiation pneumonitis.
14. Have an ongoing or active infection, including, but not limited to, the requirement for intravenous (IV) antibiotics.
15. Have a known history of human immunodeficiency virus (HIV) infection. Testing is not required in the absence of history.
16. Have a known or suspected hypersensitivity to brigatinib or its excipients.
17. Have a known or suspected hypersensitivity to crizotinib or its excipients.
18. Have malabsorption syndrome or other gastrointestinal (GI) illness or condition that could affect oral absorption of the study drug.
19. Have any condition or illness that, in the opinion of the investigator, would compromise patient safety or interfere with evaluation of the study drug.

11 STUDY PROCEDURES

The *screening period* begins when the informed consent form is signed, and continues until randomization. The *follow-up period* begins at the end of treatment and continues until patient contact discontinues.

11.1 Study Procedure Descriptions

The study procedures to be performed at screening and throughout the Randomized Phase of the study are listed in Table 3 (Schedule of Events), which is meant to provide a convenient display of the timing and scope of required assessments expected at each visit, but does not provide a comprehensive description of each assessment. A complete list of all study-related assessments as well as a detailed description of what is expected in the assessment is included below. Investigators must be familiar with the details of this section and use it in conjunction with the table to adequately carry out the required study assessments. All study assessments should occur within ±3 days of the scheduled study visit unless otherwise noted in the Schedule of Events descriptions or table. A cycle is defined as 28 days.

Crossover in Arm B (crizotinib) to brigatinib is permitted, at the investigator's discretion with the sponsor's medical monitor approval, for patients who have experienced objective progression documented by BIRC or the investigator. Patients who crossover from crizotinib to brigatinib treatment (Crossover Phase) will adhere to the Schedule of Events listed in Table 4. All assessments for the Crossover Phase will be performed as described below for the Randomized Phase, except as noted.

The following list describes the footnotes for Table 3 and Table 4.

1. Screening

Patients with known locally advanced or metastatic ALK+ NSCLC and no history of prior ALK-targeted TKI treatment can be considered for screening. Screening assessments must be performed no more than 14 days prior to Day 1, with the exception of tumor imaging assessment, where the allowable window is 21 days prior to first dose of study drug (Cycle 1, Day 1). However, whenever feasible, baseline imaging should be performed as close as possible to Cycle 1, Day 1.

Screening physical examination, ECOG Performance Status assessments, and clinical laboratory assessments (hematology, chemistry, testosterone [male patients], insulin, and pregnancy test) do not need to be repeated on Cycle 1, Day 1 if they were performed for screening within 7 days prior to Cycle 1, Day 1 AND, in the opinion of the investigator, there is no reason to believe they have substantially changed. The pregnancy test may be repeated at any time during the study if the patient or the investigator has cause to believe that the patient may be pregnant. If screening laboratory assessments need to be repeated on Cycle 1, Day 1, they should be obtained before starting treatment.

2. Informed Consent

Informed consent, documented by a signed and dated consent form, must be obtained prior to any screening activities that are not otherwise considered part of normal patient care. Informed consent can be signed prior to the 14-day screening period window.

3. Randomization

Specific instructions for randomization will be supplied in the Study Reference Manual. Randomization procedures should be performed following completion of all eligibility assessments and determination of patient eligibility and prior to the initiation of assigned treatment.

4. Demographics

Demographic information will be obtained at screening and consists of the patient's age, sex, race, and ethnicity (as allowed by local law and regulations).

5. Medical/Surgical History

A complete medical history will be taken at screening. Information to be documented includes relevant past illnesses, including other cancers, smoking history, ongoing medical conditions, and surgical procedures (not related to the primary diagnosis).

6. Diagnosis and Cancer History

The initial cancer diagnosis and the current cancer stage at the time of screening, along with tumor histology and all sites of disease, should be recorded. Any previously identified mutations other than ALK, and the dates of identification, must be recorded.

7. Prior Cancer Therapy

Prior cancer therapy history will be taken at screening and includes cancer-related surgical procedures, radiation, and systemic therapies. Surgical procedures include curative and palliative, as well as diagnostic procedures (e.g., biopsy). Radiation will include both definitive and palliative treatment. Systemic therapy should include all regimens given, type of regimen (e.g., neo-adjuvant, adjuvant, for advanced or metastatic disease), number of cycles administered for each regimen, each drug name in a regimen, the start and stop dates of each drug, the best response to the regimen, and the reason for discontinuation. Experimental or investigational therapy history must also be recorded.

8. ALK Mutation Status

Regarding current and past ALK mutation history, any previously identified mutations, and the dates of identification, must be recorded at screening. This includes ALK rearrangements by FISH, ALK abnormalities by other methods including immunohistochemistry (IHC), and ALK point mutations.

Patients entering the study must either have a history of a positive Vysis® ALK Break-Apart FISH Probe Kit test or Ventana ALK (D5F3) CDx Assay, or must have history of ALK-positivity by another test and submit tissue samples for central laboratory analysis using an FDA-approved test. Specifications regarding handling and processing of tissue for this test are described under Item 21 below (Tumor Tissue Samples) and in the Study Reference Manual.

9. Physical Examination

A complete physical examination must be performed at screening, the extent of which should be consistent with medical history and the patient's underlying disease. Subsequent physical examinations may be directed to relevant findings. Of note, due to adverse reactions reported during treatment with crizotinib and brigatinib, investigators are cautioned to monitor patients for signs of vision dysfunction. For new or worsening severe vision disorders, ophthalmological evaluation consisting of best corrected visual acuity, retinal photographs, visual fields, optical coherence tomography (OCT) and other evaluations should be performed. The End-of-Treatment physical examination should be a complete physical examination. The physical examination 30 days after last dose may be directed to any relevant findings.

10. Vital Signs

Vital signs include temperature, pulse, respiratory rate, and blood pressure (when patient is seated). In addition, the screening assessment must include height and weight. Vital signs should be repeated on Cycle 1, Day 1, prior to first dose, regardless of the time from screening. Vital signs will also be assessed per the Schedule of Events throughout the study.

11. ECOG Performance Status

The patient's performance status must be assessed using the ECOG performance scale during screening ECOG performance status will also be assessed per the Schedule of Events throughout the study. The ECOG performance scale is provided in Appendix B.

12. Hematology

Hematology laboratory measurements include complete blood count (CBC) with 5-part differential and platelet count. Cycle 1, Day 1 hematology blood draws should be performed prior to the first dose of study drug. Hematology laboratory measurements will be assessed per the Schedule of Events throughout the study.

13. Chemistry

Serum chemistry laboratory assessments include: sodium, potassium, chloride, bicarbonate (or total carbon dioxide), blood urea nitrogen (BUN, or urea), albumin and total protein, creatinine, bilirubin (at least total and direct or total and indirect), ALT (SGPT), AST (SGOT), alkaline phosphatase, magnesium, phosphorous, calcium, lactate dehydrogenase (LDH), creatine kinase (CK), uric acid, amylase, lipase, and glucose. Cycle 1, Day 1 serum chemistry blood draws should be performed prior to the first dose of study drug. Chemistry laboratory measurements will also be assessed per the Schedule of Events throughout the study.

14. Insulin

Serum insulin and glucose should be measured concurrently. Cycle 1, Day 1 insulin blood draws should be performed prior to the first dose of study drug. Insulin will also be assessed per the Schedule of Events throughout the study.

15. Testosterone Level (males only)

In male patients, serum testosterone should be measured at screening and throughout the study per the Schedule of Events.

16. Electrocardiogram

All ECGs must be 12-lead ECGs and will be assessed per the Schedule of Events throughout the study.

Additional ECGs may be performed at the investigator's discretion to ensure patient safety. In particular, ECG monitoring should be performed during the study if a patient has, during the study, been prescribed medication that can prolong the QT interval or medication that can potentially alter the QT interval (other than medications explicitly prohibited).

For consistency, the Fridericia correction ($QTcF = QT\ interval/(RR)^{1/3}$ interval) method must be used for all calculations of heart rate-corrected QT (calculated) (QTc) intervals.

17. Adverse Events

Adverse events (AEs) are to be recorded continuously throughout the entire study until at least 30 days after the last dose of study drug and graded per NCI CTCAE v4.0 (See Appendix A). It is expected that new and updated AEs and concomitant medications reported within the treatment period, ongoing AEs thought to be at least possibly study-drug related, and all ongoing SAEs should be followed at least every 4 weeks until they resolve to baseline (or to NCI CTCAE v4.0 grade ≤1), stabilize, or are considered to be chronic/irreversible.

18. Concomitant Medications

Concomitant treatments for all ongoing medical history conditions or AEs, as well as prophylactic treatments and supplements, must be reported from the date the informed consent is signed until at least 30 Days After Last Dose, and for all concomitant treatments related to serious or study drug-related toxicities until the medication is no longer taken or until patient contact discontinues.

19. Pregnancy Test

The pregnancy test must be a beta-human chorionic gonadotropin (β-HCG) test, and either urine or serum can be used. Women who are not of childbearing potential (status post-hysterectomy, status post-bilateral oophorectomy, or post-menopausal [defined as amenorrhea for at least 12 months]) and men do not need to have the test performed. The test must be known to be negative prior to the study drug administration and be performed within 7 days prior to first study drug administration (Cycle 1, Day 1). Women of childbearing potential at study start must also complete the pregnancy test once every 12 weeks thereafter and at the End-of-Treatment. Additional pregnancy testing should be performed if recommended or required per local guidelines or regulations.

20. Disease Assessment CT/MRI, Brain MRI

At screening, disease assessment must include imaging of the chest and abdomen (including adrenal glands), using appropriate radiological procedures (computed tomography [CT] scans or magnetic resonance imaging [MRI] with contrast, unless contrast media is contraindicated). Contrast-enhanced MRI of the brain (such as gadolinium) is required at screening for all patients. All radiographic images (e.g., CT scan, MRI) performed during the study will be submitted to the imaging core laboratory for central review. Patients must have at least 1 measurable lesion per RECIST v1.1. Previously irradiated lesions may not be used for target lesions, unless there is unambiguous radiological progression after radiotherapy. Brain lesions may be used as target lesions provided they are ≥10 mm and have not been: 1) previously treated with whole brain radiation therapy (WBRT) within 3 months, or 2) previously treated by stereotactic radiosurgery (SRS) or surgical resection.

Disease assessment by CT and MRI scans will be performed at screening and at 8-week intervals thereafter (on Day 28 [±3 days] of every even-numbered cycle), through Cycle 14 after the initial dose of study drug, and every 3 cycles thereafter until End-of-Treatment. Imaging of chest, abdomen and brain will occur at each assessment for all patients. More frequent imaging is recommended at any time if clinically indicated; confirmation of CR or PR should be performed at least 4 weeks after initial response. Imaging assessment will also be performed at End-of-Treatment if more than 4 weeks have passed since the last imaging assessment. The same imaging modality at the same institution should be used at each assessment, if possible.

A patient randomized to Arm B (crizotinib) with objective disease progression assessed by the BIRC may crossover to brigatinib treatment, at the investigator's discretion with the sponsor's medical monitor approval (see Section 13.1.2). The disease assessment which documents progression will serve as the new baseline for the crossover portion of the study. The investigator will reevaluate the patient for target and non-target lesions, according to RECIST criteria, based on the disease assessment scans showing the initial progression. A crossover patient need not repeat imaging assessments before Crossover Cycle 1, Day 1, unless the disease assessment is incomplete, or occurred >21 days prior to Crossover Cycle 1, Day 1 (in which case, disease assessments must be repeated and will serve as the new baseline). If the disease assessment is incomplete, the site will obtain any missing radiographic imaging (e.g., MRI of the brain) prior to initiation of treatment with brigatinib. Disease assessment by CT and MRI scans will be performed at 8-week intervals thereafter (on Day 28 [±3 days] of every even-numbered cycle), through Cycle 14 after the initial dose of brigatinib, and every 3 cycles thereafter until End-of-Treatment. Imaging assessment will also be performed at End-of-Treatment if more than 4 weeks have passed since the last imaging assessment. The same imaging modality at the same institution should be used at each assessment, if possible.

For patients who discontinue the study drug due to a reason other than progressive disease, additional tumor assessment should be documented, if available, until disease progression or start of another systemic anti-cancer therapy. For patients who continue brigatinib beyond BIRC-assessed progressive disease at the investigator's discretion, imaging will continue with a similar assessment schedule. If the patient experiences symptomatic

deterioration, it is strongly recommended that additional imaging studies be performed to confirm progressive disease.

21. Tumor Tissue Samples

Mandatory Tumor Tissue From All Patients at Screening:

Formalin-fixed paraffin-embedded (FFPE) tumor tissue that was acquired prior to randomization must be provided for exploratory molecular genetic analysis. This tissue can be from the primary tumor or from a biopsied metastasis. A pathologist should assess the tissue sample to ensure adequate tumor tissue is available based on the minimum requirements described in the Study Reference Manual.

For patients who do not have a prior positive result from the Vysis® ALK Break-Apart FISH Probe Kit or Ventana ALK (D5F3) CDx Assay, this sample will be used for central testing by an FDA-approved test and exploratory biomarker studies. For patients with a prior positive result for one of the FDA-approved tests, this sample will be used for exploratory biomarker studies.

Optional Tumor Tissue at Time of Disease Progression:

For patients who consent, a biopsy will be performed at the time of progression on brigatinib (for patients in Arm A) or crizotinib (for patients in Arm B) and at the time of subsequent progression on brigatinib (for patients in Arm B after crossover to brigatinib). FFPE tumor tissue should be sent to the central laboratory. This tumor tissue will be used for exploratory molecular genetic analysis.

22. CCI [redacted]

23. CCI [redacted]

CCI

[redacted]

24. Quality of Life Assessments

The EORTC QLQ-C30 and EORTC QLC-LC13 questionnaires will be administered at baseline, per the Schedule of Events throughout the study, and at the 30 days after last dose visit. The questionnaires should be administered to patients when they arrive for their scheduled visits, **prior to** any clinical measurements, assessments, evaluations, or procedures being performed.

25. End-of-Treatment Randomized Phase (Arms A and B)/Crossover Phase (Arm B Only)

The End-of-Treatment visit should be performed within 2 weeks (14 days) of the patient's last dose of study drug or the patient/investigator decision to discontinue study drug—whichever occurs later. Physical examinations, laboratory tests (hematology, chemistry, and insulin), and ECG may be omitted if they had been previously performed within 2 weeks since the last assessments and if, in the investigator's judgment, significant change is unlikely.

Patients in Arm B (crizotinib) who crossover to brigatinib should complete the assessments for the End-of-Treatment visit for crizotinib. These assessments will serve as baseline assessments for the Crossover Phase. After a minimum 10-day washout period, and a maximum of 28 days, the patient will start brigatinib treatment on Crossover Cycle 1, Day 1, and will follow the schedule of events for the crossover phase as described in Table 4. For these patients, End-of-Treatment assessments must also be performed within 2 weeks (14 days) of the patient's last dose of brigatinib or the patient/investigator decision to discontinue study drug—whichever occurs later.

26. 30 Days After Last Dose

The 30 Days After Last Dose assessments must be performed 30 days (±7 days) after the last dose of study drug. Physical examinations and laboratory tests (hematology, chemistry, and insulin), and ECG can be omitted if the visit occurs within 10 days of the End-of-Treatment assessment and there have been no clinically significant findings. Any new systemic anticancer therapies that the patient has begun receiving since the end of treatment should be reported at this visit. For both the End-of-Treatment and 30 Days After Last Dose assessments, information may be collected from tests performed for the study or as part of the patient's routine medical care.

Patients in Arm B (crizotinib) who crossover to brigatinib will not be required to have a 30 Days After Last Dose visit after discontinuing crizotinib. A 30 Day After Last Dose visit will be required when brigatinib is discontinued.

27. Follow-up

Patients will be followed throughout the study, as per Table 3 and Table 4. The follow-up assessments (i.e., contacting the patient for survival and subsequent anticancer therapy) must be performed every 12 weeks (±14 days) after the End-of-Treatment for the last study

drug administered (e.g., after End-of-Treatment with brigatinib for patients who crossover in Arm B). The allowable window for follow-up assessments is 14 days. All new systemic anticancer therapies should be reported. Follow-up will continue for approximately 3 years after the last patient is randomized into the study.

Table 3 Schedule of Events - Randomized Phase

	Screening Period	During Treatment and Through 30 Days After Last Dose									Follow-up Period
Assessment	Screening[1]	Cycle 1			Cycle 2		Every 4 weeks	Every 8 or 12 weeks	End-of-Treatment[25]	30 Days After Last Dose[26]	Follow-up[27]
Day (D)	D-14 to D0	D1	D8	D15	D1	D15					
Informed Consent[2]	X										
Randomization[3]	X										
Demographics[4]/Medical/Surgical History[5]	X										
Diagnosis and Cancer History[6]/ Prior Cancer Therapy[7]	X										
ALK Mutation Status[8]	X										
Tissue for central ALK FISH Testing[21]	X										
Physical Examination[9]	X	X[1]	X*	X	X		X		X	X	
Vital Signs[10]	X	X	X	X	X		X		X	X	
ECOG Performance Status[11]	X	X[1]			X		X		X	X	
Hematology[12]	X	X[1]		X	X		X		X	X	
Chemistry[13]	X	X[1]		X	X	X**	X		X	X	
Insulin[14]	X	X		X	X		X		X	X	
Testosterone Level (males only)[15]	X	X[1]			X		X		X	X	
Pregnancy Test[19]	X	X[19]					X (every 12 weeks)[19]		X[19]		
Electrocardiogram (ECG)[16]	X	X			X		X		X	X	
Brigatinib (Arm A only)		ONCE-DAILY ORAL DOSE									
Crizotinib (Arm B only)		TWICE-DAILY ORAL DOSE									
Adverse Events[17]	THROUGHOUT STUDY										
Concomitant Treatments[18]	THROUGHOUT STUDY										
Disease Assessment [20]	X							X	X		
CCI [redacted]											
Tissue Sample At Disease Progression[21]									X		
Quality of Life Assessments[24]	X	X			X		X		X	X	
Subsequent Anticancer Therapy/Survival											X

*Assessment for early pulmonary symptoms must be performed during the visit on Day 8.
**Only AST, ALT and Total Bilirubin are required on Cycle 2, Day 15.
For footnotes, see Section 11.1.

Table 4 Schedule of Events – Brigatinib Crossover Phase (Arm B Only)

	Crizotinib Washout	During Treatment and Through 30 Days After Last Dose							Follow-up Period
Assessment	10-28 Days After Last Crizotinib Dose	Cycle 1 Crossover C1D1			Every 4 Weeks	Every 8 or 12 Weeks	End-of-Treatment[25]	30 Days After Last Dose[26]	Follow-up[27]
Day (D)		D1	D8	D15					
Physical Examination[9]		X	X*	X	X		X	X	
Vital Signs[10]		X	X	X	X		X	X	
ECOG Performance Status[11]		X			X		X	X	
Hematology[12]		X		X	X		X	X	
Chemistry[13]		X		X	X		X	X	
Insulin[14]		X		X	X		X	X	
Testosterone Level (males only)[15]		X			X		X	X	
Pregnancy Test[19]		X[19]				X (every 12 weeks)[19]	X[19]		
Electrocardiogram (ECG)[16]		X			X		X	X	
Brigatinib		ONCE-DAILY ORAL DOSE							
Adverse Events[17]		THROUGHOUT STUDY							
Concomitant Treatments[18]		THROUGHOUT STUDY							
Disease Assessment [20]						X	X		
CCI [redacted]									
Tissue Sample Upon Disease Progression							X		
Quality of Life Assessments[24]		X			X		X	X	
Subsequent Anticancer Therapy/Survival									X

*Assessment for early pulmonary symptoms must be performed during the visit on Day 8.
For footnotes, see Section 11.1.
Note: All assessments for the Crossover Phase will be performed as described for the Randomization Phase, except as noted.

11.2 Screening Period

The screening period begins when the informed consent form is signed, and continues until randomization. See Section 11.1 for further details.

11.3 Screen Failures

Patients who have signed informed consent and subsequently fail to meet the inclusion and/or exclusion criteria are defined as screen failures. Once the investigator determines that screening will not continue for a patient and the patient will not be enrolled in the study, the screen failure should be documented on the Eligibility Criteria eCRF within 5 days. For all screen failures, the investigator is to maintain a screening log that documents the patient initials and reason(s) for screen failure. A copy of the log should be retained in the investigator's study files. Patients who screen fail may later be re-screened with prior sponsor approval.

11.4 Treatment Through 30 Days after Last Dose of Study Drug

This period begins when the patient receives the first dose of study drug.

Assessments required during this period for the Randomized Phase and the Crossover Phase are shown in Table 3 and Table 4, respectively. A detailed description of procedures and timing is provided in Section 11.1.

Note: clinical laboratory assessments do not need to be repeated on Cycle 1, Day 1 if they were performed for screening within 7 days prior to Cycle 1, Day 1.

11.5 End-of-Treatment or Early Termination

End-of-Treatment is defined as the point when or the patient and investigator decide to end study drug (which may be after a dose interruption). Assessments required at Randomized Phase End-of-Treatment are shown in Table 3. A detailed description of procedures and timing is provided in Section 11.1.

Patients in Arm B (crizotinib) who crossover to brigatinib should complete the assessments for the End-of-Treatment visit for crizotinib. These assessments will serve as baseline assessments for the Crossover Phase. After a minimum 10-day washout period, the patient will start brigatinib treatment on Crossover Cycle 1, Day 1, and will follow the schedule of events for the crossover phase as described in Table 4.

11.6 30 Days After Last Dose

Assessments required at 30 Days After Last Dose for the Randomized Phase and the Crossover Phase are shown in Table 3 and Table 4, respectively. A detailed description of procedures and timing is provided in Section 11.1.

Patients in Arm B (crizotinib) who crossover to brigatinib will not be required to have a 30 Days After Last Dose visit for crizotinib.

11.7 Follow-up Period Procedures

The follow-up period for a patient begins after End-of-Treatment (i.e., when all study drug has been discontinued) and continues until patient contact ceases (for approximately 3 years after the last patient has enrolled).

Assessments required for the Follow-up Period for the Randomized Phase and the Crossover Phase are shown in Table 3 and Table 4, respectively. A detailed description of procedures and timing is provided in Section 11.1.

11.8 Study Duration

11.8.1 Approximate Duration of Patient Participation

Patients will continue to be dosed with brigatinib (Arm A) or crizotinib (Arm B) until they experience BIRC-assessed disease progression or intolerable toxicity. Treatment with brigatinib may be continued after progression, at the discretion of the investigator, if there is still evidence of clinical benefit. At the discretion of the investigator with the sponsor's medical monitor approval, patients who experience BIRC-assessed disease progression on crizotinib may crossover to treatment with brigatinib (see Section 13.1.2 for details on treatment continuation after progression). On average, a patient is expected to participate in this study for approximately 4 years.

11.8.2 Approximate Duration of Study

The total estimated duration of the study is approximately 4.5 years, including 1.5 years to accrue patients, with approximately 3 years for treatment and follow-up of the last patient. Since the study met the statistical significance at the first interim analysis and the primary endpoint was consistent at the second interim analysis, the study will be closed approximately 3 years after the last patient enrolled. Patients will be allowed to receive brigatinib beyond the 3-year treatment period until they experience disease progression, they discontinue treatment for other reasons, or the study is closed.

11.9 Patient Discontinuation

Patients in the Randomized Phase will be discontinued from further study drug administration (brigatinib or crizotinib) in the event of any of the following:

- Intolerable toxicity as determined by the investigator
- Progression of disease requiring an alternate therapy, in the opinion of investigator

  Note: Treatment of patients in Arm A with brigatinib may be continued, despite BIRC-assessed progression by RECIST v1.1, at the discretion of the investigator, if there is still evidence of clinical benefit. In this clinical trial, patients in Arm B may not continue treatment with crizotinib beyond BIRC-assessed progression. Crossover of patients in Arm B to treatment with brigatinib may occur at the time of BIRC-assessed progression on crizotinib, at the discretion of the investigator with the sponsor's medical monitor approval.

- Progression of disease as assessed by the BIRC for patients in Arm B for which crossover is not being considered
- Entry into another therapeutic clinical study or start of new anticancer therapy
- Significant deviation from the protocol or eligibility criteria, in the opinion of the sponsor's medical monitor or investigator
- Noncompliance with study or follow-up procedures
- Pregnancy
- Patient withdrawal of consent or decision to discontinue participation
- Termination of the study by the sponsor
- Any other reason that, in the opinion of the investigator, would justify removal of the patient from the study

Patients in the Crossover Phase will be discontinued from further brigatinib administration in the event of any of the following:

- Intolerable toxicity as determined by the investigator
- Progression of disease requiring an alternate therapy, in the opinion of investigator

  Note: Treatment of patients with brigatinib may be continued, despite progression by RECIST v1.1, at the discretion of the investigator, if there is still evidence of clinical benefit.
- Entry into another therapeutic clinical study or start of new anticancer therapy
- Significant deviation from the protocol or eligibility criteria, in the opinion of the sponsor's medical monitor or investigator
- Noncompliance with study or follow-up procedures
- Pregnancy
- Patient withdrawal of consent or decision to discontinue participation
- Termination of the study by the sponsor
- Any other reason that, in the opinion of the investigator, would justify removal of the patient from the study

In the event that a patient is withdrawn from the study, every effort must be made by the investigator to document and report the reasons for withdrawal as thoroughly as possible. The reason(s) for withdrawal must be clearly reported on the appropriate page of the patient's electronic case report form (eCRF). An eCRF must be completed for any patient randomized and an End-of-Treatment reason must be recorded for any patient who is randomized, regardless of whether they receive study drug.

If a patient is discontinued from treatment for any reason, every effort must be made to perform all End-of-Treatment and 30 Days After Last Dose assessments per the schedule of events (Table 3 or Table 4). In the event that the patient fails to return for the necessary visit(s), an effort must

be made to contact the patient to determine the reason, and this information should be recorded in the appropriate source record and reported as a deviation.

All patients who permanently discontinue from study drug will be followed-up for survival and collection of new systemic anti-neoplastic therapies administered every 12 weeks after End-of-Treatment until patient contact ceases (for approximately 3 years after the last patient has been randomized).

11.10 Study or Site Termination

If the sponsor, investigator, medical monitor, or regulatory agencies discover conditions during the study that indicate that the study or site should be terminated, this action may be taken after appropriate consultation between the sponsor and the investigator (in the case of site termination). Conditions that may warrant termination of the study include, but are not limited to:

- The discovery of a serious, unexpected, or unacceptable risk to subjects enrolled in the study
- The decision on the part of the sponsor to suspend or discontinue testing, evaluation, or development of the study drug
- Duration of the study extends greater than 3 years after the last patient is randomized
- Submission of knowingly false information from the research facility to the sponsor, medical monitor, or regulatory authorities
- Insufficient adherence to protocol requirements

Study termination and follow-up will be performed in compliance with the conditions set forth in the guidelines for Good Clinical Practice (GCP), International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

11.11 Sample Collection, Storage, and Shipping

All samples must be collected by appropriately trained individuals. Use of Universal Precautions is recommended when collecting any biological specimen. Plasma samples must be stored at or below -20ºC until shipment. Specific instructions regarding the handling and shipment of these specimens will be provided in the Study Reference Manual.

12 EFFICACY AND SAFETY ASSESSMENTS

12.1 Efficacy Assessments

Tumor response assessments will be performed every 8 weeks and evaluated per RECIST v1.1 (see Appendix C) by the BIRC and the investigator until BIRC-assessed disease progression. Tumor response (CR or PR) should be confirmed ≥4 weeks after initial response. For patients who discontinue the study treatment due to a reason other than BIRC-assessed progressive disease, additional tumor assessment should be documented, if available, until disease progression or start of another systemic anti-cancer therapy. For patients in Arm A who continue brigatinib beyond disease progression, tumor assessments will continue to be performed every 8 weeks. For patients in Arm B who crossover to brigatinib after BIRC-assessed progression on

crizotinib, the tumor response assessment with BIRC-assessed progression will be re-evaluated per RECIST v1.1 criteria as a new baseline for the Crossover Phase unless >21 days prior to Crossover C1D1, which will require a new disease assessment prior to starting brigatinib. Tumor response assessments will be performed every 8 weeks and evaluated per RECIST v1.1 by the BIRC and the investigator until BIRC-assessed disease progression. For patients who discontinue the study drug due to a reason other than BIRC-assessed progressive disease, additional tumor assessment should be documented, if available, until disease progression or start of another systemic anti-cancer therapy.

OS will be followed for approximately 3 years after the last patient has been randomized.

12.2 Safety Assessments

Safety assessments will include physical and laboratory examinations, vital signs, and ECGs. AEs will be graded according to the NCI CTCAE, v4.0 (see Appendix A and the Study Reference Manual). Safety assessments and their timing are outlined in Section 11.1.

12.3 Pharmacokinetic Assessments

Sparse plasma brigatinib concentration data obtained from this study will be included in integrated population PK analyses, along with data from study AP26113-11-101 and study AP26113-13-201, with the objective of further characterizing the plasma PK of brigatinib in the intended patient population, and to assess exposure-response (for efficacy) and exposure-safety relationships in patients receiving brigatinib.

Plasma PK samples may also be used for exploratory biomarker evaluations.

12.4 Exploratory Biomarker Evaluations in Tissue and Blood

CCI

[redacted]

12.5 Patient Reported Symptoms and Quality of Life Assessments

Patient-reported symptoms and HRQoL will be collected by administering the EORTC QLQ-C30 (v3.0) and the lung cancer-specific module (the QLQ-LC13, v3.0) questionnaires, which have been studied extensively, are validated, and are suitable for use in global clinical studies. The questionnaires will be administered to patients in their local language, if available.

On the study days they are administered, the questionnaires should be completed by patients prior to any testing or discussion with the physician.

The EORTC QLQ-C30 is a cancer-specific questionnaire initially tested in lung cancer patients (Aaronson et al, 1993). The EORTC QLQ-C30 will be scored for 5 functional scales (physical,

role, cognitive, emotional, and social functioning); 3 symptom scales (fatigue, pain, and nausea/vomiting); and a global health status/QoL scale. Six single-item scales also are included (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).

The LC13 module was constructed in parallel with the core QLQ-C30. It comprises 13 questions assessing lung cancer associated symptoms (cough, hemoptysis, dyspnea, and site specific pain), treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy, and alopecia), and use of pain medication (Aaronson et al, 1996; Bergman et al, 1994). It is scored as a set of single items.

Note: Signs and symptoms assessed with the patient-reported outcome (PRO) questionnaires will not be considered AEs unless entered as such into the eCRF.

13 STUDY TREATMENTS

13.1 Study Drug

Brigatinib is an investigational drug that will be administered only to eligible enrolled patients at qualified centers (e.g., listed on the FDA Form 1572).

13.1.1 Treatment Administration

Patients will be randomized 1:1 to receive brigatinib (Arm A) or crizotinib (Arm B).

In Arm A, brigatinib will be administered orally at a dose of 90 mg QD for 7 days followed by 180 mg QD continuously, with or without food. Patients will take the prescribed dose with water (recommended 240 mL).

In Arm B, crizotinib orally will be administered as 250 mg BID, with or without food. Patients will take the prescribed dose with water (recommended 240 mL).

Patients who forget to take their scheduled dose of study drug should be instructed not to make up the missed dose. A missed dose is defined as a dose not taken within 6 hours of the intended scheduled administration. Missed doses should be recorded in an appropriate source record (e.g., clinic chart), patient diary card, and study drug administration eCRF.

Study drug administration will continue until the patient dies, meets another reason for treatment discontinuation, or the trial ends.

13.1.2 Continuation of Treatment after Disease Progression

Patients in the Randomized Phase will continue to be dosed with brigatinib (Arm A) or crizotinib (Arm B) until they experience BIRC-assessed disease progression or intolerable toxicity or are discontinued for other reasons. In certain circumstances, at the discretion of the treating investigator, brigatinib may be continued after progressive disease has been identified.

Continued Therapy at the Time of Disease Progression in Arm A

Patients in Arm A who experience BIRC-assessed disease progression may continue to be treated with brigatinib if, in the opinion of the treating investigator, they continue to experience clinical benefit. Patients in Arm B may not continue treatment with crizotinib on study after BIRC-assessed disease progression.

Crossover from Arm B (Crizotinib) to Brigatinib Treatment After Disease Progression

Crossover to brigatinib is permitted, at the investigator's discretion with the sponsor's medical monitor approval, for patients treated with crizotinib in Arm B who experience objective disease progression assessed by the BIRC or investigator. Instructions for receiving notification of disease progression assessed by the BIRC can be found in the Study Reference Manual.

All patients who crossover to brigatinib from crizotinib must have a washout period of at least 10 days between treatments. Brigatinib will be administered at a dose of 90 mg QD for 7 days followed by 180 mg QD continuously, with or without food. Patients will take the prescribed dose with water (recommended 240 mL). Brigatinib treatment will start on Crossover Cycle 1, Day 1, as shown in Table 4. A cycle of therapy in the Crossover Phase will comprise 28 days of treatment.

13.1.3 Management and Dose Modification Recommendations for Treatment-Related Adverse Events

The following sections provide recommended dose modification guidelines for treatment-related AEs observed with brigatinib and crizotinib administration.

Dose interruptions or reductions should be implemented for patients who experience treatment-related AEs, upon clinical judgment of the investigator. Study drug administration may be delayed for up to 28 days to allow for improvement or resolution of the event. If an AE does not resolve to grade 1 or less after dose interruption for more than 28 days, the sponsor's medical monitor must be contacted.

Comprehensive assessments of any study drug-related AEs (i.e., adverse drug reactions) experienced by the patient will be performed throughout the course of the study. The severity of the event, as well as clinical judgment, will be utilized to determine appropriate management of the patient for any AE experienced while participating in this study.

Any medication, including those administered for therapy of symptoms considered associated with study drug administration, should be reported on the appropriate concomitant medication page of the patient's eCRF.

13.1.3.1 Management and Dose Modification Recommendations for Treatment-Related Adverse Events in Patients Receiving Brigatinib (Arm A or Crossover Patients)

13.1.3.1.1 Adverse Events within the First 7 Days of Treatment with Brigatinib, Prior to Dose Escalation

Criteria for dose modification of general treatment-related adverse events (excluding pneumonitis) in the first 7 days of treatment prior to dose escalation are provided in Table 5. Criteria for dose modification of general treatment-related adverse events (excluding pneumonitis) after dose escalation are provided in Section 13.1.3.1.3.

In study AP26113-11-101, pulmonary events occurring within the first 7 days of treatment with brigatinib, consistent in some cases with pneumonitis, were observed shortly after treatment initiation in 4% of patients who had received brigatinib at a starting dose of 90 mg QD (including patients who escalated to 180 mg QD after 7 days). No such events were observed in the 7 days after escalation to 180 mg QD. Events included the acute onset of symptoms of

dyspnea, cough, chest tightness, and fever. Pulmonary symptoms have been observed after a single dose of brigatinib in some patients. The pulmonary symptoms are associated in more severe cases with hypoxia and chest CT findings of ground glass opacities consistent with pneumonitis, and in these cases constituted SAEs. These events have been managed with treatment interruption and medical management as clinically indicated (e.g., steroids, antibiotics). Most events resolved with interruption or discontinuation of brigatinib. Three fatal pulmonary events (including hypoxia, pneumonia, and adult respiratory distress syndrome) starting within the first 7 days of treatment were observed in study AP26113-11-101. Upon resumption of dosing, some patients had events recur while others did not have recurrence with continued dosing. As such, investigators and patients must be aware that pneumonitis-like events may present as early as 24 to 48 hours of initial dosing.

Pulmonary events occurring within the first 7 days of treatment, including, but not limited to, dyspnea, hypoxia, dry cough, chest tightness, and presumptive lung infection (pneumonia) should be monitored and reported. To reiterate, some events occur after a single dose of brigatinib, and physicians should be aware of this possibility and discuss it with patients. Newly developed or worsening of pulmonary symptoms in the first week of study drug administration specifically with hypoxia and ground glass opacity on radiographic imaging indicative of interstitial lung disease or pneumonitis could suggest a relationship to brigatinib. Other etiologies, including pulmonary embolism and infectious pneumonia, should be ruled out if possible. If no evidence of other etiology is identified, a causal relationship to brigatinib should be considered.

The management of new or worsening pulmonary symptoms within the first 7 days of brigatinib treatment should include drug interruption, monitoring of oxygen saturation, radiographic evaluation of the chest, and appropriate work up for infectious or other etiology, with high dose corticosteroids, supplemental oxygen therapy, and empiric antibiotics as indicated. After drug interruption and workup of symptoms, dose modification should be accomplished according to the recommendations in Table 5. If the work up reveals documented hypoxia and/or radiologic evidence of interstitial or ground glass changes, or result in an SAE, the pulmonary events should be treated according to Table 6 in Section 13.1.3.1.2 (Pneumonitis).

Table 5 Brigatinib Dose Modification Recommendations for Treatment-Related Adverse Events (Excluding Pneumonitis) Prior to Dose Escalation to 180 mg QD (i.e., First 7 Days of Treatment)

Toxicity Grade per CTCAE v4.0	Recommended Action	Criteria for Dose Escalation
Hematologic Toxicity		
Grade 1 or Grade 2	Continue at 90 mg QD	Escalate to 180 mg QD on Day 8, as scheduled
Grade 3	Hold until event is ≤ grade 2, or has returned to baseline, then resume at 90 mg QD	No dose escalation
Grade 4	Hold until event is ≤ grade 2, or has returned to baseline, then resume at 90 mg QD	No dose escalation
Nonhematologic Toxicity		
Grade 1	Manage the toxicity with supportive care while continuing at 90 mg QD	Escalate to 180 mg QD on Day 8, as scheduled
Grade 2 (≤3 days)	Manage the toxicity with supportive care while continuing at 90 mg QD	If the event is controlled to no worse than grade 1 at Day 8, escalate to 180 mg QD, as scheduled
Grade 2 (for >3 days, despite optimal supportive care)	Hold until event is ≤ grade 1, or has returned to baseline, then resume at 90 mg QD	If no recurrence of grade 2 after 90 mg QD for 7 days, escalate to 120 mg QD. Do not escalate to 180 mg QD. If recurrence of grade 2 after 90 mg QD, no escalation
Grade 3	Hold until event is ≤ grade 1, or has returned to baseline, then resume at 90 mg QD	No dose escalation
Grade 4	Hold until event is ≤ grade 1, or has returned to baseline, then resume at 60 mg QD	No dose escalation
Bradycardia (heart rate less than 60 beats per minute [bpm])		
Grade 1	Continue at 90 mg QD	Escalate to 180 mg QD on Day 8, as scheduled
Grade 2 or Grade 3	Withhold until recovery to ≤ grade 1 or to heart rate 60 bpm or above Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at 90 mg QD upon recovery to ≤ grade 1 or to heart rate 60 bpm or above If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume at 60 mg QD upon recovery to ≤ grade 1 or to heart rate 60 bpm or above.	No dose escalation
Grade 4	Discontinue treatment if no contributing concomitant medication is identified If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at 60 mg QD upon recovery to ≤ grade 1 or to heart rate 60 bpm or above with frequent monitoring.	No dose escalation

13.1.3.1.2 Pneumonitis

Pneumonitis and interstitial lung disease are known side effects of TKIs used in NSCLC, generally occurring later in the course of therapy. Crizotinib has been associated with severe, life-threatening, or fatal treatment-related pneumonitis in clinical trials with a frequency of 4 in 255 (1.6%) patients (XALKORI® USPI, Pfizer, Inc.). Other TKIs used in the treatment of NSCLC have similar adverse reactions. Drug-related pneumonitis may be associated with signs and symptoms such as dyspnea, hypoxia, cough, hemoptysis, and fever as well as radiologic evidence of parenchymal or interstitial changes.

The diagnosis of pneumonitis and determination of causal relationship to the drug is often confounded by the underlying disease (especially lymphangitic carcinomatosis) and other factors such as lung infection and radiation effect due to non-specific signs and symptoms as well as similar radiological appearance. Pneumonitis should be suspected when such signs and symptoms develop or in asymptomatic patients when a new ground glass opacity or interstitial infiltration is noted in imaging studies. If a patient is considered to have the potential diagnosis of drug-related pneumonitis, physical examination, assessment of oxygen saturation, evaluation for infectious etiologies, and thoracentesis, bronchoscopy, or open lung biopsy should be considered to reach a diagnosis. If the causality is at least possibly related to the study drug, management of pneumonitis, including dose interruption and potential discontinuation, as presented in Table 6 (during first 7 days of treatment prior to escalation to 180 mg QD) and Table 7 (after escalation to 180 mg QD), is required.

Table 6 Brigatinib Dose Modification Recommendations for Treatment-Related Pneumonitis Occurring Prior to Dose Escalation to 180 mg QD (i.e., First 7 Days of Treatment)

Toxicity Grade	Recommended Action
Grade 1	Withhold the dose until pneumonitis returns to grade 0 (baseline), then resume at 90 mg and do not escalate. If pneumonitis recurs, permanently discontinue treatment.
Grade 2	Withhold the dose until pneumonitis returns to Grade 0, then resume at 60 mg and do not escalate. If pneumonitis recurs, permanently discontinue treatment.
Grade 3	Permanently discontinue treatment.
Grade 4	Permanently discontinue treatment.

Table 7 Brigatinib Dose Modification Recommendations for Treatment-Related Pneumonitis Occurring After Dose Escalation to 180 mg QD

Toxicity Grade	Recommended Action
Grade 1	Withhold the dose until pneumonitis returns to grade 0 (baseline), then resume at the same dose. If pneumonitis recurs, permanently discontinue treatment.
Grade 2	Withhold the dose until pneumonitis returns to Grade 0. Resume at 120 mg QD. If pneumonitis recurs, permanently discontinue treatment.
Grade 3	Permanently discontinue treatment.
Grade 4	Permanently discontinue treatment.

13.1.3.1.3 Dose Modification Recommendations for Treatment-Related Adverse Events (Excluding Pneumonitis) After Dose Escalation to 180 mg QD

Criteria for dose modification of general treatment-related adverse events (excluding pneumonitis) after dose escalation are provided in Table 8.

Table 8 Dose Modification Recommendations for Treatment-Related Adverse Events (Excluding Pneumonitis) after Dose Escalation to 180 mg QD*

Toxicity Grade per CTCAE v4.0	Recommended Action
Hematologic Toxicity	
Grade 1 or Grade 2	Continue at current dose
Grade 3	When the current dose is 180 mg QD: Hold until event is ≤ grade 2, or has returned to baseline Resume at 180 mg or 120 mg QD at the discretion of the investigator Upon recurrence at 180 mg QD: Hold until event is ≤ grade 2, or has returned to baseline Resume at 120 mg QD When the current dose is 120 mg QD: Hold until event is ≤ grade 2, or has returned to baseline Resume at 90 mg QD When the current dose is 90 mg QD: Hold until event is ≤ grade 1, or has returned to baseline Resume at 60 mg QD after recovery, or discontinue at the discretion of the investigator When the current dose is 60 mg QD: Consider discontinuing treatment
Grade 4	When the current dose is 180 mg QD: Hold until event is ≤ grade 2, or has returned to baseline Resume at 120 mg QD after recovery When the current dose is 120 mg QD: Hold until event is ≤ grade 2, or has returned to baseline Resume at 90 mg QD after recovery When the current dose is 90 mg QD: Hold until event is ≤ grade 1, or has returned to baseline Resume at 60 mg QD after recovery, or discontinue at the discretion of the investigator When the current dose is 60 mg QD: Consider discontinuing treatment

Toxicity Grade per CTCAE v4.0	Recommended Action
Nonhematologic Toxicity	
Grade 1 or Grade 2	Manage the toxicity with supportive care while continuing at the same dose
Grade 3	When the current dose is 180 mg QD: Hold until event is ≤ grade 1, or has returned to baseline Resume at 180 mg QD or 120 mg QD at the discretion of the investigator Upon recurrence at 180 mg QD: Hold until event is ≤ grade 1, or has returned to baseline Resume at 120 mg QD When the current dose is 120 mg QD: Hold until event is ≤ grade 1, or has returned to baseline Resume at 90 mg QD after recovery When the current dose is 90 mg QD: Hold until event is ≤ grade 1, or has returned to baseline Resume at 60 mg QD after recovery, or discontinue at the discretion of the investigator When the current dose is 60 mg QD: Consider discontinuing treatment
Grade 4	When the current dose is 180 mg QD: Hold until event is ≤ grade 1, or has returned to baseline Resume at 120 mg QD, or discontinue, at the discretion of the investigator When the current dose is 120 mg QD: Hold until event is ≤ grade 1, or has returned to baseline Resume at 90 mg QD, or discontinue, at the discretion of the investigator When the current dose is 90 mg QD: Hold until event is ≤ grade 1, or has returned to baseline Resume at 60 mg QD after recovery, or discontinue at the discretion of the investigator When the current dose is 60 mg QD: Consider discontinuing treatment
Bradycardia (heart rate less than 60 beats per minute [bpm])	
Grade 1	Continue at current dose
Grade 2 or Grade 3	Withhold until recovery to ≤ grade 1 or to heart rate 60 bpm or above Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recover to ≤ grade 1 or to heart rate 60 bpm or above If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume at reduced dose upon recovery to ≤ grade 1 or to heart rate 60 bpm or above: When the current dose is 180 mg QD, resume at 120 mg QD When the current dose is 120 mg QD, resume at 90 mg QD When the current dose is 90 mg QD, resume at 60 mg QD When the current dose is 60 mg QD, discontinue treatment

Toxicity Grade per CTCAE v4.0	Recommended Action
Grade 4	Discontinue treatment if no contributing concomitant medication is identified If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at reduced dose upon recovery to ≤ grade 1 or to heart rate 60 bpm or above with frequent monitoring: When the current dose is 180 mg QD, resume at 120 mg QD When the current dose is 120 mg QD, resume at 90 mg QD When the current dose is 90 mg QD, resume at 60 mg QD When the current dose is 60 mg QD, discontinue treatment
* Apply these recommendations either after dose escalation was accomplished, or after dose reduction for grade 3 or grade 4 toxicity was implemented resulting in no dose escalation.	

13.1.3.1.4 Management of Additional Selected Treatment-Related Adverse Events

Hypertension

Blood pressure should be monitored and recorded at each visit. Hypertension detected by at least 2 blood pressure measurements should be graded according to NCI CTCAE, v4.0, which defines hypertension as a disorder characterized by a pathological increase in blood pressure: a repeated elevation in the blood pressure exceeding 140 mmHg for systolic and over 90 mmHg for diastolic. For patients who either develop hypertension or experience worsening hypertension during treatment with study drug, at the discretion of the investigator, aggressive antihypertensive medication should be initiated or optimized to achieve target blood pressure before interruption or dose reduction of the study drug. If hypertension is persistent despite adequate antihypertensive therapy—including titration of antihypertensive medication or introduction of additional antihypertensive medications—or if grade 4 hypertension develops, dose interruption and reduction is recommended according to Dose Modification Guidelines for general nonhematologic AEs in Table 5 and Table 8.

Bradycardia

Heart rate should be monitored and recorded at each visit. Brigatinib should be avoided in combination with other agents known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine and digoxin) to the extent possible. For symptomatic bradycardia, dose interruption and reduction is recommended according to Table 5 and Table 8.

Nausea and Emesis

Nausea should be treated with standard-of-care anti-emetics. Prophylactic ant-emetics may be used.

Diarrhea

For grade 1 diarrhea, symptomatic care such as loperamide (Imodium®, McNEIL-PPC, Inc.) may be given, or no intervention may be undertaken, according to the investigator's clinical judgment. For grade 2 diarrhea, administer loperamide at 4 mg, then 2 mg every 2 to 4 hours until the patient is symptom-free for 12 hours. No dose modification is necessary unless the patient does not tolerate brigatinib or the symptom recurs. For grade ≥3 despite loperamide,

treatment will be withheld until recovery to grade ≤1. Secondary prophylaxis in patients who have experienced diarrhea with brigatinib treatment is allowed. Other medications and supportive care may be added according to the institution's standard of care.

Visual Disturbance

In patients with new onset or worsening severe (grade ≥3) visual disturbance, ophthalmological evaluation should be performed. Visual disturbance should be managed as described in Table 5 and Table 8 (under Nonhematologic Toxicity).

13.1.3.2 Management and Dose Modification Recommendations for Treatment-Related Adverse Events in Patients Receiving Crizotinib (Arm B)

13.1.3.2.1 Management of Selected Adverse Events

Hepatotoxicity

Drug-induced hepatotoxicity with fatal outcome has occurred in patients treated with crizotinib. These cases have occurred during crizotinib treatment in less than 1% of patients in clinical trials. Concurrent elevations in ALT greater than 3×ULN and total bilirubin greater than 2×ULN without elevated alkaline phosphatase have been observed in less than 1% patients in clinical trials. Grade 3 and 4 elevations in liver function tests were generally reversible upon dosing interruption. When hepatotoxicity occurs, crizotinib should be temporarily suspended, dose reduced, or permanently discontinued as described in Table 9.

Interstitial Lung Disease

Severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with crizotinib. These cases generally occurred within 2 months after the initiation of treatment. Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis. Other potential causes of ILD/pneumonitis should be excluded, and crizotinib should be discontinued in patients diagnosed with drug-related ILD/pneumonitis.

QT Prolongation

QTc prolongation can occur in patients treated with crizotinib. Crizotinib should be avoided in patients with congenital long QT syndrome. Crizotinib should be discontinued in patients who develop QTc greater than 500 msec or greater than or equal to 60 msec change from baseline with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia. Crizotinib should be withheld in patients who develop QTc greater than 500 msec on at least 2 separate ECGs until recovery to a QTc less than or equal to 480 msec, then resumed at a reduced dose as described in Table 9.

Bradycardia

Symptomatic bradycardia can occur in patients treated with crizotinib. Crizotinib should be avoided in combination with other agents known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine and digoxin) to the extent possible. Heart rate and blood pressure should be monitored regularly. Symptomatic bradycardia should be managed as described in Table 9.

Visual Loss

Grade 4 visual field defect with vision loss has been reported in less than 1% of patients in clinical trials of crizotinib. In patients with new onset or worsening severe (Grade ≥ 3) visual disturbance, ophthalmological evaluation should be performed. Visual loss should be managed as described in Table 9.

13.1.3.2.2 Dose Modification Recommendations for Treatment-Related Adverse Events in Patients Receiving Crizotinib (Arm B)

Guidelines for dose modification of crizotinib treatment-related AEs are outlined in Table 9 and are based on the European Medicines Agency (EMA) Summary of Product Characteristics (SmPC) for crizotinib (XALKORI® SmPC, Pfizer, Inc.). Unless otherwise noted, reduce dose as below, if one or more dose reductions are necessary due to adverse reactions of grade 3 or 4 severity, as defined by NCI CTCAE v4.0.

- First dose reduction: crizotinib 200 mg BID
- Second dose reduction: crizotinib 250 mg QD
- Permanently discontinue if unable to tolerate crizotinib 250 mg QD

Table 9 Crizotinib Dose Modification Recommendations for Treatment-Related Adverse Events

Toxicity Grade per CTCAE v4.0	Recommended Action
Hematologic Toxicities except lymphopenia (unless associated with clinical events e.g., opportunistic infections)	
Grade 1or Grade 2	Manage the toxicity with supportive care while continuing at the same dose
Grade 3	Withhold until recovery to ≤grade 2, then resume at the same dose schedule
Grade 4	Withhold until recovery to ≤grade 2, then resume at 200 mg BID[b]
Non-Hematologic Toxicities	
Grade 3 or 4 ALT or AST elevation with ≤ Grade 1 total bilirubin	Withhold until recovery to ≤ Grade 1 or baseline, then resume at 250 mg QD and escalate to 200 mg BID if clinically tolerated[c]
Grade 2, 3, or 4 ALT or AST elevation with concurrent Grade 2, 3 or 4 total bilirubin elevation (in the absence of cholestasis or haemolysis)	Permanently discontinue
Any grade drug-related interstitial lung disease/pneumonitis	Withhold if ILD/pneumonitis is suspected, and permanently discontinue if treatment-related ILD/pneumonitis is diagnosed
Grade 3 QTc prolongation	Withhold until recovery to ≤ Grade 1, check and if necessary correct electrolytes, then resume at 200 mg twice daily[c]
Grade 4 QTc prolongation	Permanently discontinue
Grade 2, 3 Bradycardia[d]	Withhold until recovery to ≤ Grade 1 or to a heart rate of 60 bpm or above Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to ≤ Grade 1 or to a heart rate of 60 bpm or above If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume at reduced dose upon recovery to ≤ Grade 1 or to a heart rate of 60 bpm or above
Grade 4 Bradycardia[d]	Permanently discontinue if no contributing concomitant medication is identified If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at 250 mg once daily upon recovery to ≤ Grade 1 or to a heart rate of 60 bpm or above, with frequent monitoring
Grade 4 Ocular Disorder (Visual Loss)	Discontinue during evaluation of severe vision loss

[a]Except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).
[b]In case of recurrence, dosing should be withheld until recovery to ≤ Grade 2, then dosing should be resumed at 250 mg once daily. Crizotinib must be permanently discontinued in case of further Grade 4 recurrence.
[c]Crizotinib must be permanently discontinued in case of further ≥ Grade 3 recurrence.
[d]Heart rate less than 60 beats per minute (bpm).

13.1.4 Re-introducing Brigatinib after Dose Interruption

If brigatinib treatment interruption lasts ≥14 days, and prior dose was >90 mg QD, patients should resume treatment at 90 mg QD for 7 days, before escalating dose back to 120 mg QD or 180 mg QD. The dose should not be escalated higher than the prior dose level before treatment interruption.

13.1.5 Re-Escalation after Dose Modification

Re-escalation after dose modification for adverse events is discouraged. However, if in the opinion of the treating investigator re-escalation is warranted, this must be undertaken after consultation with the sponsor. To be a candidate for re-escalation, the AE that led to dose modification must not have recurred, and no other AEs of grade 3 or 4 must have been observed during the preceding 28 days.

13.2 Prior and Concomitant Treatment(s)/Therapy

History of prior cancer therapy will be recorded at screening, and concomitant cancer therapy will be recorded during the study on the appropriate eCRF for each patient.

Reasonable efforts will be made to collect information on all prior cancer therapy received by the patient (e.g., surgeries, chemotherapy, radiotherapy, immunotherapy, biologics). The information must be obtained from the patient's medical chart and recorded on the appropriate eCRF.

Palliative therapy and supportive care are permitted during the study for management of symptoms and underlying medical conditions that may develop during the study. Once a patient has begun treatment, a condition may arise that requires the initiation of a new concomitant treatment. Patients with CNS lesions requiring local radiotherapy such as SRS are allowed to continue study drug after appropriate interruption, as determined by the investigator with sponsor agreement; however, for analysis purposes, these patients will be considered to have PD.

Concomitant medications for all ongoing medical history conditions or AEs must be reported from the date the informed consent is signed until at least the 30 Days After Last Dose assessments, and for all concomitant medications related to serious or study drug-related toxicities until the medication is no longer taken or until patient contact discontinues.

13.3 Prohibited Treatment(s)/Therapy

The following concurrent medications or procedures are prohibited for the duration of the study:

1. Any other systemic anticancer therapy including, but not limited to: chemotherapeutic agents, immunotherapy, biological response modifiers (excluding growth factors), radiotherapy, and/or systemic hormonal therapy (**with the exception of** local therapies, such as SRS, used for palliative or symptomatic control of existing lesions, with appropriate treatment interruption at the discretion of the investigator). Use of any other investigational drug or device;
2. Medications that are known to be associated with the development of Torsades de Pointes (see Appendix E). Medications that prolong the QT interval, but are not known to be associated with Torsades de Pointes, should be avoided, but are not prohibited;

3. Extensive surgery requiring in-patient care (patients may have an interruption in therapy for 14 days should emergency surgery be required).

If a patient's clinical condition requires treatment with one of the prohibited classes of medications specified above, the clinical details of the situation should be discussed with the sponsor's medical monitor at the earliest possible time to determine whether it is safe for the patient to continue treatment.

13.4 Potential Drug Interactions

Brigatinib

In vitro studies with human liver microsomes indicate that cytochrome P450 (CYP) 2C8 and CYP3A4 are involved in the human metabolism of brigatinib. Medications and dietary (grapefruit-containing products) or herbal products (St John's Wort) that are strong inhibitors or inducers of CYPs, in particular, CYP2C8 or CYP3A4, should be avoided (see Appendix D).

Brigatinib is not a reversible inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5, with IC_{50} values of >70 µM. Brigatinib is also not a metabolism-dependent or a time-dependent inhibitor of the CYPs tested. Hence, drug-drug interactions (DDIs) due to inhibition of CYPs by brigatinib are unlikely.

Crizotinib (XALKORI® USPI, Pfizer, Inc.)

Crizotinib is predominantly metabolized by CYP3A4/5. Coadministration of crizotinib with strong CYP3A inhibitors increases crizotinib plasma concentrations. Avoid concomitant use of strong CYP3A inhibitors, including, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, and voriconazole. Avoid grapefruit or grapefruit juice which may also increase plasma concentrations of crizotinib. Exercise caution with concomitant use of moderate CYP3A inhibitors.

Crizotinib inhibits CYP3A both in vitro and in vivo. Coadministration of crizotinib with strong CYP3A inducers decreases crizotinib plasma concentrations. Avoid concomitant use of strong CYP3A inducers, including, but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's Wort.

Avoid concomitant use of CYP3A substrates with narrow therapeutic range, including, but not limited, to alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus in patients taking crizotinib. If concomitant use of these CYP3A substrates with narrow therapeutic range is required in patients taking crizotinib, dose reductions of the CYP3A substrates may be required due to adverse reactions.

In vitro studies in human hepatocytes have indicated that crizotinib may induce pregnane X receptor (PXR)- and constitutive androstane receptor (CAR)-regulated enzymes (e.g., CYP3A4, CYP2B6, CYP2C8, CYP2C9, UGT1A1). Caution should be exercised in administering crizotinib in combination with medicinal products that are predominantly metabolized by these enzymes. The effectiveness of concomitant administration of oral contraceptives may be reduced.

13.5 Treatment Compliance

Patients will be provided a diary card or equivalent where the date of study drug administration will be recorded. Complete instructions will be provided with the Study Reference Manual. Patients who forget to take their dose should not make up the missed dose. A missed dose is defined as a dose not taken within 6 hours of the intended scheduled administration. Any missing doses must be recorded in an appropriate source record (e.g., clinic chart), patient diary card, and study drug administration eCRF. Training of patients should be documented in the appropriate source record (e.g., clinic chart). When possible, patients should take the study drug under observation during scheduled study visits to the clinic. The investigator is responsible for ensuring that the patient diary card(s) are retained and noted in source documentation.

13.6 Treatment Supply

Upon receipt of clinical study materials and/or study drug, the investigator or designee must verify that the shipment was received as stated on the clinical supply shipment form enclosed within each shipment. The form is then to be returned to the clinical supply distributor as instructed on the form. If there are any discrepancies with the shipment, the sponsor should be contacted immediately (contact information is listed on the clinical supply shipment form). A copy of this form must be retained in the site files.

13.6.1 Formulation, Packaging and Labeling

Brigatinib

Brigatinib drug product is supplied as film-coated tablets, containing 30 mg, 90 mg, or 180 mg of brigatinib active pharmaceutical ingredient. Other ingredients are typical pharmaceutical excipients (lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, colloidal silica, and magnesium stearate). The tablet coating is composed of typical pharmaceutical grade coating components (talc, polyethylene glycol, polyvinyl alcohol, and titanium dioxide). The drug product is manufactured under current Good Manufacturing Practice in accordance with approved procedures. Brigatinib will be supplied in white high-density polyethylene bottles with induction sealed caps or blister packs.

Bottle or blister pack labels will bear the appropriate label text as required by governing regulatory agencies. At a minimum, such text will include product name, product strength, number of tablets, and lot number.

Crizotinib (XALKORI® USPI, Pfizer, Inc.)

Crizotinib drug product is supplied as gelatin capsules containing either 200 mg or 250 mg of crizotinib active pharmaceutical ingredient. Other inactive ingredients include colloidal silicone dioxide, microcrystalline cellulose, anhydrous dibasic calcium phosphate, sodium starch glycolate and magnesium stearate. The gelatin capsule is composed of gelatin, titanium oxide, and red iron oxide.

Bottle or blister pack labels will bear the appropriate label text as required by governing regulatory agencies. At a minimum, such text will include product name, product strength, number of tablets, and lot number.

13.6.2 Preparation and Dispensing

The study pharmacist or designee at the site will be responsible for handling and dispensing brigatinib and crizotinib and completing associated documentary paperwork. Supplies are shipped to the investigative site at appropriate intervals, depending on patient accrual. The site must use an appropriate dispensing log/accountability form provided by the sponsor or an acceptable substitute used by the site. Each time study medication is dispensed for a patient, the following information must be recorded: the patient's initials, the patient's study number, drug product strength (e.g., 30 mg), quantity dispensed with the corresponding lot number, date of dispensation, and the initials of the person dispensing the drug. These logs are to be maintained by the study pharmacist in the pharmacy throughout the duration of the study and will be periodically verified by a representative of the sponsor.

13.6.3 Treatment Storage and Accountability

The recommended storage condition for brigatinib is under 30°C. Do not refrigerate or freeze.

The recommended storage condition for crizotinib is room temperature 20º to 25º C; excursions permitted between 15º and 30º C.

The investigator is responsible for ensuring that the study drug provided to the patient and returned from the patient are reconciled and noted in source documentation.

All used bottles or blister packs of study drug must be returned to the study sponsor or destroyed in an appropriate manner according to the standard practice at each study center. Destruction of such supplies will be documented, and a representative of the sponsor will verify disposition records.

During the study and at termination, patients must return all unused study drug supplies and the return of these unused study drug supplies must be recorded. Returned supplies must not be re-dispensed.

No other utilization of brigatinib or crizotinib intended for use in this study is authorized by the sponsor. The principal investigator or his/her designee will be responsible for the appropriate handling and disposition of residual study drug. Each site is responsible for proper and careful destruction of study drug returned by patients.

Periodically, throughout and at the conclusion of the study, a representative of the sponsor will conduct an inventory of unused study drug. At the completion of the study, a final study drug accountability review will be conducted. Any discrepancies must be investigated and all unused study drug must be destroyed on site per the standard operating procedures of the investigative site.

14 ADVERSE EVENT REPORTING

14.1 Adverse Events

14.1.1 Adverse Event Definition

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including

an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product whether or not considered related to the medicinal product. Any worsening of a preexisting condition which is temporally associated with the use of the study drug (i.e., occurs after the first dose of study drug) is also an AE.

Adverse Events include:

- Abnormal test findings, according to the following criteria:
  - Test results associated with accompanying symptoms that are considered clinically significant in the opinion of the investigator.
  - Test results that require additional diagnostic testing (other than merely repeating an abnormal test) or medical/surgical intervention.
  - Test results that lead to a change in study drug dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
  - Test results considered to be an AE by the investigator or sponsor.
- Changes in physical examination findings
- Other untoward medical events, regardless of their relationship to the study drug, such as injury, events that require surgery, accidents, or apparently unrelated illnesses, and
- Hypersensitivity

Additionally, AEs may include signs or symptoms resulting from:

- Drug overdose (events occurring from a medication error or overdose of a product or products whether accidental or intentional)
- Drug withdrawal
- Drug abuse
- Drug misuse
- Drug interactions
- Drug dependency
- Exposure during breastfeeding
- Exposure in utero

14.1.2 Performing Adverse Events Assessments

All observed or volunteered AEs, regardless of treatment group or suspected causal relationship to the investigational product(s), will be reported, as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious AE (SAE; see Section 14.2.1) requiring immediate notification to ARIAD Pharmaceuticals, Inc. (ARIAD) or its designated representative.

14.1.3 Reporting Period

All AEs (serious and non-serious) should be recorded on the AE eCRF for all patients beginning at the time of signing the informed consent form and concluding 30 days following the last dose of the assigned study drug in the study or the investigator/patient decision to discontinue treatment, whichever occurs later.

Once a patient is deemed a screen failure, AE collection is no longer required (see Section 11.3).

Any ongoing AEs (serious and non-serious) after the reporting period should be followed until they resolve to baseline, stabilize, or are considered to be chronic/irreversible.

New SAEs after reporting period: There is no requirement to monitor subjects for SAEs after end of study. Investigators in the European Economic Area (EEA) are obligated to report SAEs that they become aware of to the sponsor even after the reporting period (reference European Commission CT-3 Section 4.4). Investigators outside the jurisdiction of the EEA are encouraged to report SAEs after the reporting period.

14.1.4 Adverse Event Severity

The severity of AEs will be assessed according to the CTCAE v4.0 (see Appendix A and the Study Reference Manual). If the AE is not defined in the CTCAE, the investigator will determine the severity of the AE based on the following definitions:

- *Mild (grade 1):* The AE is noticeable to the patient but does not interfere with routine activity;
- *Moderate (grade 2):* The AE interferes with routine activity but responds to symptomatic therapy or rest;
- *Severe (grade 3):* The AE significantly limits the patient's ability to perform routine activities despite symptomatic therapy;
- *Life-Threatening (grade 4):* The patient is at immediate risk of death;
- *Death (grade 5):* The patient dies as a direct result of the complication or condition induced by the AE.

14.1.5 Causality

The investigator's assessment of causality must be provided for all AEs (serious and non-serious). An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the study drug (i.e., brigatinib or crizotinib) caused or contributed to the AE.

In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and on the SAE form and report such an assessment in accordance with the SAE reporting requirements.

The investigator will use medical consideration and use the following categories of causality to determine the relatedness of an AE with the study drug based on the following definitions. Not all criteria in each category of relatedness must be present.

Definitely Not Related (not drug related)

- The patient did not receive study drug

OR

- The temporal sequence of the AE onset relative to the administration of the study drug is not reasonable

OR

- There is another obvious cause of the AE

Probably Not Related (not drug related)

- There is evidence of exposure to study drug
- There is another more likely cause of the AE
- Dechallenge (if performed) is negative or ambiguous
- Rechallenge (if performed) is negative or ambiguous

Possibly Related (drug related)

- There is evidence of exposure to study drug
- The temporal sequence of the AE onset relative to administration of the study drug is reasonable
- The AE could have been due to another equally likely cause
- Dechallenge (if performed) is positive

Probably Related (drug related)

- There is evidence of exposure to study drug
- The temporal sequence of the AE onset relative to administration of the study drug is reasonable
- The AE is more likely explained by the study drug than by another cause

Definitely Related (drug related)

- There is evidence of exposure to study drug
- The temporal sequence of the AE onset relative to administration of the study drug is reasonable
- Dechallenge is positive
- Rechallenge (if feasible) is positive
- The AE shows a pattern consistent with previous knowledge of the test drug or a test drug class

14.1.6 Expectedness

The expectedness of an SAE is assessed by the sponsor in the overall classification of SAEs for regulatory reportability. The Investigator Brochure section "Summary of Data and Guidance for the Investigator" will be used as the reference for determination of expectedness and risk assessment for brigatinib. The current SmPC for Xalkori (crizotinib) will be used as the reference safety information for determination of expectedness for crizotinib.

14.2 Serious Adverse Events

The definitions and reporting requirements of ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A, will be followed.

14.2.1 Serious Adverse Event Definition

The investigator or the sponsor may determine the seriousness of an AE based on the following:

An AE is considered an SAE if at least one of the following conditions applies:

- *Death:* An AE that results in death is any patient death within 30 days of the last dose of study drug administration. The cause of death or AE that resulted in a fatal outcome is the SAE.
- *Life-threatening AE:* An AE that places the patient, in the view of the investigator or the sponsor, at immediate risk of death from the event as it occurred (i.e., this does not include an event that had it occurred in a more severe form might have caused death)
- *Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions*: Any substantial disruption of a person's ability to conduct normal life functions
- *Inpatient hospitalization or prolongation of existing hospitalization:* Hospitalization refers to admission of a patient into a hospital for any length of time.
- *A congenital anomaly/birth defect:* A fixed, permanent impairment established at or before birth
- *Cancer:* Occurrence or diagnosis of a new cancer during the study is considered an SAE; a new cancer is a cancer that is histopathologically different than the cancer under study in the study (i.e., does not include metastatic or progressive disease)
- *Important medical event:* Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not result in death, be life-threatening, or require hospitalization. However, if it is determined that the event may jeopardize the patient and/or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical events should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse.

14.2.1.1 Progression of the Malignancy Under Study (including signs and symptoms of progression)

Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the eCRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as an AE.

14.2.1.2 Hospitalizations

Adverse events (reported from clinical studies) that require hospitalization or prolongation of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a health care facility meets these criteria. Adverse events that require emergency room care that do not result in hospital admission are not SAEs unless assessed by the investigator to be an important medical event. Hospitalization does not include the following:

- Hospice facilities
- Respite care
- Skilled nursing facilities
- Nursing homes
- Routine emergency room admissions, and
- Same day surgeries (as outpatient/same day/ambulatory procedure)

Hospitalization or prolongation of hospitalization in the absence of a precipitating AE is not in itself an SAE. Examples include:

- Social admission (e.g., patient has no place to sleep)
- Protocol-specified admission during a clinical study (e.g., for a procedure required by the study protocol)
- Optional admission not associated with a precipitating AE (e.g., for elective cosmetic surgery that was planned prior to study enrollment [appropriate documentation is required for these cases])
- Hospitalization or prolongation of hospitalization for scheduled therapy of the target malignancy of the study is not considered an SAE

14.2.2 Reporting Serious Adverse Events

Regardless of causality, SAEs must be reported (see Section 14.2.4 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee within 24 hours of becoming aware of the event. This will be done by transmitting an electronic data capture (EDC) SAE report. If transmission of an EDC SAE report is not feasible, then a facsimile of the completed Takeda paper-based SAE form will be sent. In case of fax, site personnel need to confirm successful transmission of all pages and include an e-mail address on the fax cover sheet so that an acknowledgment of receipt can be returned via e-mail within 1 business day. A sample of the paper-based SAE form and processing directions are in the Study Manual. Information in the SAE report or form must be consistent with the data provided on the eCRF.

14.2.3 Information to be Provided by the Investigator for a Serious Adverse Event

The sponsor or designee will require all of the following information about the patient and the event:

- Investigator identification
- Patient identification code (e.g., sex, age, or date of birth)
- Information on study drug (e.g., start/stop date, dose and frequency of study drug administered)
- Description of event

In addition to the above information, the sponsor will require the investigator's assessment of the following:

- Severity of the SAE
- Relationship of the SAE to the study drug
- Outcome of the SAE

14.2.4 Follow-up Information on a Serious Adverse Event

The investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded on the electronic study case report forms (eCRF) where safety data may also be recorded (e.g., AE CRF). The investigator is responsible for management of the patients through the course of the event. There should be routine follow-up through and including a minimum 30 days after the last administration of study drug or the investigator/patient decision to discontinue treatment, whichever occurs later, in all patients in order to monitor for the occurrence of SAEs. If an SAE continues after the 30-day evaluation period, then the patient must be followed until the event resolves or stabilizes without further involvement expected. The sponsor's medical monitor may specify a longer period of time if required to assure the safety of the patient.

14.2.5 Expedited Reporting of Suspected Unexpected and Serious Adverse Reactions (SUSARs)

ARIAD, as study sponsor, is responsible for reporting suspected, unexpected and serious adverse reactions (SUSARs) involving the study drug to all regulatory authorities and participating investigators in accordance with ICH Guidelines and/or local regulatory requirements, as applicable. In addition, ARIAD, or authorized designee, will be responsible for the submission of safety letters to central independent ECs (IECs).

The sponsor will notify investigators of all reportable SAEs. This notification will be in the form of an expedited safety report. Upon receiving such notices, the investigator must review and retain the notice with other study-related documentation.

The investigator and IRB/EC will determine whether the informed consent requires revision. The investigator should also comply with the IRB/EC procedures for reporting any other safety information.

Suspected serious adverse reactions and other significant safety issues reported from the investigational product development program will be reported by the sponsor or its designated representative, either as expedited safety reports and/or in aggregate reports, to the relevant competent health authorities in all concerned countries.

14.3 Other Safety Issues

14.3.1 Pregnancy and Breastfeeding

Female patients of childbearing potential and fertile male patients will be informed as to the potential risk of conception while participating in this study and will be advised that they must use highly effective contraception listed below (i.e., results in a low failure rate when used consistently and correctly) during the dosing period and for a period of at least 4 months after the end of treatment with brigatinib and at least 3 months after the end of treatment with crizotinib.

Highly effective methods include:

- intrauterine device (IUD)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence

Adequate contraception during and after treatment with crizotinib and brigatinib should be used as oral contraceptives may be ineffective. A pregnancy test will be performed on each pre-menopausal female patient of childbearing potential immediately prior to the first dose of study drug, once every three cycles while on treatment, and again at treatment discontinuation during the End-of-Treatment visit. A negative pregnancy test must be documented prior to administration of study drug.

If a patient is confirmed pregnant during the study, study drug administration must be discontinued immediately. The investigator must immediately notify the sponsor medical monitor of this event and record the pregnancy on the Pregnancy Form. Initial information regarding a pregnancy must be immediately forwarded to ARIAD Pharmacovigilance and Risk Management or its designated representative.

The investigator must immediately report follow-up information to the sponsor regarding the course of the pregnancy, including perinatal and neonatal outcome, regardless of whether the patient has discontinued participation in the study. If the pregnancy results in the birth of a child, additional follow-up information may be requested. If the pregnancy results in spontaneous abortion or stillbirth, the event should be reported as an SAE.

Pregnancy outcomes also must be collected for the female partners of any male patients who took study drug in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

It is not known whether brigatinib passes into the breast milk. Mothers should not breastfeed while receiving study drug.

14.3.2 Overdose

An overdose is defined as the accidental or intentional ingestion or infusing of any dose of study drug that exceeds the dose described in the protocol.

All overdoses should be recorded on the Overdose Form and forwarded to ARIAD Pharmacovigilance and Risk Management, or its designated representative, within 24 hours. An overdose should be reported even if it does not result in an AE. If an overdose results in an AE, the AE should be reported on the AE eCRF. The dose administered should be documented on the Study Drug Administration eCRF.

15 PLANNED STATISTICAL METHODS

15.1 General Considerations

Descriptive statistics (such as means, medians, standard deviations, and ranges for continuous data and percentages for categorical data) will be used to summarize patient characteristics, study drug administration/compliance, and safety parameters. Data will also be displayed graphically, where appropriate. For the purposes of this protocol and all analyses, unless otherwise specified, a month is defined as 28 days, the same length as a cycle of treatment for both brigatinib and crizotinib.

15.2 Analysis Populations

Intent–to-Treat (ITT) Population: The ITT population includes all patients randomized to each regimen regardless of whether they are ALK+ by the Vysis® ALK Break Apart fluorescence in situ hybridization (FISH) Probe Kit or the Ventana ALK (D5F3) CDx Assay, or a local test other than FISH and IHC, or whether they receive study drug or adhere to the assigned dose. The primary analyses of efficacy will be based on the ITT population.

Treated population: The treated population for each regimen includes all patients receiving at least one dose of study drug.

Safety will be analyzed using the treated population.

Per-protocol population: The per-protocol population will exclude all patients in the treated population who do not meet key entry criteria, have no measurable disease at baseline, or have no adequate post-baseline response assessment unless the reason is death or early discontinuation due to disease progression. Additional analyses may also be performed excluding patients who were not confirmed as ALK+ (locally or centrally) by an FDA approved test.

Further criteria for the per-protocol population and the sensitivity analyses of the primary endpoint and selected secondary efficacy endpoints using this population will be detailed in the statistical analysis plan (SAP).

15.3 Study Endpoints

15.3.1 Primary Endpoint

The primary endpoint is PFS, as assessed by the BIRC, per RECIST v1.1.

15.3.2 Secondary Endpoints

Secondary endpoints of the study include:

1. Confirmed ORR, as assessed by the BIRC, per RECIST v1.1
2. Confirmed intracranial ORR, as assessed by the BIRC
3. Intracranial PFS, as assessed by the BIRC
4. OS
5. Duration of response, as assessed by the BIRC
6. Time to response, as assessed by the BIRC
7. Disease control rate, as assessed by the BIRC
8. Safety and tolerability
9. Change from baseline scores in global health status/QOL assessed with the EORTC QLQ-C30 (v3.0), and time-to-deterioration in dyspnea assessed with the EORTC QLQ-LC13 (v3.0)

15.3.3 Exploratory Endpoints

CCI

[redacted]

15.4 Determination of Sample Size

For the purposes of this sample size calculation, the median PFS for crizotinib is estimated as 10 months (Solomon et al, 2014). Approximately 270 patients will be randomized in a 1:1 fashion to receive brigatinib or crizotinib. A total of 198 events (progression or death among the randomized patients) will provide 90% power to detect a clinically meaningful 6-month improvement in PFS (hazard ratio=0.625). This power projection is based on a 2-sided log-rank test and is controlled at the 2-sided 0.043 level, adjusting for the proposed interim analysis plan. The number of events is fixed, but the enrollment number may change based on an assessment of the overall event rate pooled across treatment groups (prior to the close of enrollment).

15.5 Efficacy Analysis

15.5.1 Definitions of Efficacy Endpoints

The primary endpoint, PFS assessed by BIRC, is defined as the time interval from the date of randomization until the first date at which disease progression is objectively documented, or

death due to any cause, whichever occurs first, in the ITT population. It will be censored for patients without documented disease progression.

Secondary efficacy endpoints for this study are defined as follows (unless otherwise stated, secondary efficacy endpoints of response will use BIRC assessments with sensitivity analyses performed using the investigator assessments):

- Confirmed ORR is defined as the proportion of the patients who are confirmed to have achieved CR or PR using RECIST v1.1 in the ITT population.
- Confirmed intracranial ORR is defined as the proportion of the patients who have achieved CR or PR in the CNS per RECIST v1.1 in randomized patients with intracranial CNS metastases at baseline.
- Intracranial PFS is defined as the time interval from the date of randomization until the first date at which CNS disease progression is objectively documented, or death due to any cause, whichever occurs first. Intracranial PFS will be assessed in patients with and without intracranial CNS metastases at baseline. It will be censored at the last disease assessment for patients without documented CNS disease progression.
- Time to response is defined as the time interval from the date randomization until the initial observation of CR or PR.
- Duration of response is defined as the time interval from the date that the criteria are first met for CR/PR (whichever is first recorded) until the first date that PD is objectively documented.
- Disease control rate is defined as the proportion of randomized patients who have achieved CR, PR, or SD (in the case of SD, criteria for SD must have been met at least once after randomization at a minimum interval of 6 weeks) after randomization.
- OS is defined as the time interval from the date of randomization until death due to any cause in the ITT population. It will be censored on the date of last contact for those patients who are alive.

Censoring for time-to-event efficacy endpoints will be detailed in the SAP.

15.5.2 Primary Efficacy Endpoint Analyses

The primary analysis of the primary endpoint will be performed using a 2-sided stratified log-rank test (stratification factors: presence of intracranial CNS metastases at baseline [Yes versus No], and prior chemotherapy for locally advanced or metastatic disease [Yes versus No]) to compare the BIRC-assessed PFS of patients randomized to brigatinib with the BIRC-assessed PFS of patients randomized to crizotinib. The overall (2-sided) Type I error rate will be controlled at 0.05. The primary analysis will be based on the ITT population. PFS will be estimated for each treatment arm using the Kaplan-Meier method (Kaplan and Meier, 1958). Additionally, hazard ratios will be estimated using the Cox regression model with the stratification factors as covariates.

Sensitivity analyses of the primary endpoint of PFS will also be performed in the following populations:

- Per-protocol population, as assessed by the BIRC
- FDA approved ALK test population, as assessed by the BIRC
- ITT population (all patients randomized to a treatment arm), as assessed by the investigator.

Subgroup analyses will be performed by baseline potential prognostic factors.

Two interim analyses are planned after approximately 50% and 75% of the total expected events (progression or death) have been observed. An O'Brien-Fleming Lan-DeMets (DeMets and Lan, 1994) alpha spending function will be used to control the overall alpha level at 0.05 2-sided.

The first interim analysis will be performed after the first 99 events have been observed. The primary endpoint of PFS will be tested at a 2-sided alpha level of 0.0042. A second interim analysis will be performed after 149 events and the primary endpoint will be tested at a 2-sided alpha level of 0.0194. The primary analysis of the primary endpoint will be performed after 198 events have been observed or at End-of-Study, whichever comes first, and will be tested at a 2-sided alpha level of 0.043. Analyses of OS will also be performed at the time of the interim analysis and at End-of-Study, if the primary endpoint is met. If the efficacy boundary is surpassed at an interim analysis, patients will remain on assigned treatments unless a survival advantage is noted.

15.5.3 Secondary Efficacy Endpoint Analyses

Confirmed ORR will be analyzed with the Mantel-Haenszel test (using the stratification factors) on the ITT population to compare the proportion of patients achieving objective response between the 2 treatment arms.

Confirmed intracranial ORR will be analyzed with the Mantel-Haenszel test (using the stratification factors) on the subset of subjects with intracranial CNS metastases at baseline, to compare the proportion of patients achieving intracranial objective response between the 2 treatment arms.

Intracranial PFS will be based on the population of patients with intracranial CNS metastases at baseline and analyzed using a 2-sided stratified log-rank test. Intracranial PFS will be estimated using the Kaplan-Meier method.

Time- to-response and duration of response will be performed on the subset of patients who achieve objective response, using the Kaplan-Meier method.

Disease control rate will be analyzed with the Mantel-Hanzel test (using the stratification factors) on the ITT population to compare the proportion of patients achieving objective response and CR, PR, or stable disease ≥6 weeks, between the 2 treatment arms.

The primary analysis of the secondary endpoint of OS will be performed using a 2-sided stratified log-rank test on the ITT population. OS will be estimated using the Kaplan-Meier method. Additional sensitivity analyses to characterize the impact of patients in Arm B who crossover to brigatinib will be performed and documented in the SAP.

For the secondary efficacy endpoints, subgroup analyses will be performed by baseline potential prognostic factors.

The primary analysis of all secondary efficacy endpoints will be performed at the time of the primary analysis of the primary endpoint.

Assuming a median OS of 30 months in the crizotinib arm, 150 events will provide approximately 20% power to demonstrate a 20% improvement (median OS of 36 months in the brigatinib arm), and approximately 14% power to demonstrate a 15% improvement (median OS of 34.5 months in the brigatinib arm). The table below shows the approximate 95% confidence intervals for the hazard ratio for each scenario under the design assumptions.

Table 10 Assumptions and Considerations for OS Endpoint

Effect Size	Number of OS Events	Power	Approx. 95% CI for HR after Specified Number of Events
1.20 (30 vs. 36 months)	150	20%	(0.87, 1.65)
1.15 (30 vs. 34.5 months)	157	14%	(0.84, 1.58)

Key secondary endpoints will be tested using a closed testing procedure to control the overall type error rate at 0.05. Analysis of a key secondary endpoint will be considered significant if the test for that endpoint and comparisons of all other secondary endpoints with a smaller rank are significant at the two-sided 0.05 significance level.

Rank-ordering of key secondary endpoints:

1. Confirmed ORR, as assessed by the BIRC, per RECIST v1.1
2. Confirmed intracranial ORR, as assessed by the BIRC
3. Intracranial PFS, as assessed by the BIRC
4. OS

15.5.4 Exploratory Efficacy Endpoint Analyses

CCI

[redacted]

15.5.5 Data Handling Rules for Efficacy Endpoint Analyses

A patient will be considered as not evaluable for response at a protocol-specified time point if no imaging/measurement is done or only a subset of lesion measurements are made, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response (i.e., if new lesions are documented). A patient will be considered to have a response if the criteria for response have been met at the

protocol-specified time points immediately before and after the time point of inevaluable response.

All patients will be assigned to one of the following best response categories: CR, PR, SD, PD, death prior to first disease assessment, or unknown (including no measurable disease at baseline, inevaluable post-baseline response, and no exposure to study drug after randomization). All patients whose best response is not CR or PR will be considered as non-responders in the calculation of ORR. Detailed data handling rules for efficacy outcomes as well as sensitivity analyses will be provided in the SAP.

15.6 Safety Analysis

Safety assessments will include physical and laboratory examinations, vital signs, and ECGs.

Adverse events will be graded according to the NCI CTCAE v4.0.

All patients who receive at least 1 dose of study drug will be evaluated for safety. For each treatment arm, the incidence rates of treatment-emergent adverse events (TEAEs), treatment-related adverse events (TRAEs), and serious treatment-emergent adverse events (SAEs) will be described by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term. The frequency of occurrence of overall toxicity, categorized by the maximum toxicity grades (severity), will also be described. Listings of laboratory test results and CTCAE grades will be generated, and descriptive statistics summarizing the changes in laboratory tests over time will be presented.

CCI

[redacted]

Exposure to study drug over time will be summarized with time on treatment, total amount of administrated treatment, dose intensity and relative dose intensity.

15.6.1 Pharmacokinetic Analysis

Summary statistics for steady-state trough (pre-dose) levels will be computed. PK data will be used in an exposure-response analysis for safety and efficacy. Details will be provided in the SAP.

15.6.2 QTcF Analysis

Descriptive statistics of maximum QTcF and change from baseline will be calculated following the ICH-E14 guidelines: the proportion of treated patients with at least 1 on-drug QTcF value >450 msec, >480 msec, and >500 msec; and the proportion of treated patients with a maximum change in QTcF from baseline >30 msec and >60 msec.

15.7 HRQoL Data Analysis

The main PRO endpoints of interest will be the Global Health Status/QoL Scale, based upon *Question 29* and *Question 30*, and the Dyspnea Scale, based on the QLQ-LC13 *Questions 3-5*. The QLQ-C30 will be scored according to the EORTC QLQ-C30 (V3) Scoring Manual (Fayers et al, 2001) including transformation of responses into scores for analysis and the handling of missing data. The EORTC QLQ-C30 (V3) Scoring Manual also includes instructions

for scoring the QLQ-LC13. Analysis of the Global Health Status/QoL Scale over time may be performed using mixed effects models that include randomized treatment group and the stratification factors used in randomization. Worsening on the Dyspnea Scale for a patient will be defined as a 50% decline from the baseline score. Time to worsening on the Dyspnea Scale will be analyzed using the same methods as for the primary analysis of PFS.

CCI

[redacted]

15.9 Protocol Deviations/Violations

To be protocol-compliant, a patient must not have any major protocol deviations during the study period. Major protocol deviations will be identified prior to database lock and will be listed in the clinical study report.

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated, it will be reported to regulatory authorities as a serious breach of GCP and the protocol.

16 QUALITY CONTROL AND QUALITY ASSURANCE

The sponsor performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any patients into this study, the sponsor personnel or its designee and the investigator will review the protocol, the Investigator's Brochure, the eCRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs. A qualified representative of the sponsor will monitor the conduct of the study by visiting the site and by contacting the site by telephone. During the visits, information recorded in the eCRFs will be verified against source documents. The sponsor's medical monitor will review the data for safety information. The sponsor's clinical data associates or designees will review the data for completeness and logical consistency. Additionally, the sponsor's clinical data associates will use automated validation programs to help identify missing data, selected

protocol violations, out-of-range data, and other data inconsistencies. Requests for data clarification or correction will be added to the electronic database and reviewed by the investigational site for resolution. The sponsor may visit the investigational site and perform a quality check of the eCRFs against source documents.

16.1 Investigators and Study Administrative Structure

The investigator must provide the sponsor with the following documents BEFORE enrolling any patients:

- An executed Clinical Trial Agreement,
- Completed and signed FDA Form 1572 or appropriate statement of investigator,
- Disclosure of financial interests in ARIAD or ARIAD products (as defined in 21 Code of Federal Regulations [CFR] part 54),
- Principal investigator's Curriculum Vitae,
- IRB/EC approval of the protocol, and
- IRB/EC approved informed consent form.

If any investigator retires, relocates, or otherwise withdraws from conducting the study, the responsibility for maintaining records may be transferred to another person (sponsor, IRB/EC, or other investigators) who accepts the responsibility. The sponsor must be notified in writing and must agree to the change. An updated FDA Form 1572 will be filed with the sponsor for any changes in study personnel reported in the current FDA Form 1572, and a disclosure of any financial interests in ARIAD or ARIAD products (as defined in 21 CFR part 54) will be required of any individual assuming the investigator's responsibilities.

16.2 Study Monitoring

This study will be monitored by representatives of the sponsor. Site visits are made before the study begins, at regular intervals during the study, and at the study closeout. Communication by telephone, mail, and e-mail may be used, as needed, to supplement site visits. The investigator and study personnel will cooperate with the sponsor, provide all appropriate documentation, and be available to discuss the study. The purpose of the site visits is to verify:

- Adherence to the protocol (the investigator should document and explain any deviation from the approved protocol).
- The completeness and accuracy of the eCRFs and the dispensing and inventory record (adequate time and space for these visits should be allocated by the investigator).
- Compliance with regulations (the verification will require comparison of the source documents to the eCRFs).

17 ETHICAL CONDUCT OF THE STUDY

This study will be conducted in accordance with the ethical standards that have their origin in the Declaration of Helsinki and that are consistent with ICH and GCP guidelines, the EMA guidance on "Ethical Considerations for Clinical Trials on Medicinal Products," and other applicable

regulatory requirements. Any significant change in the study protocol will require an amendment, which will be submitted to competent authorities and IRB/IEC for review and approval per applicable guidance and regulations.

Nothing in this protocol or the regulations is intended to limit the authority of a physician to provide emergency medical care under applicable regulations. In addition, the investigator should be aware that some regulations require that he/she permit regulatory agencies to conduct inspections and review records pertaining to this clinical investigation.

17.1 Institutional Review Board or Ethics Committee Approval

The protocol and the informed consent document must have the initial and at least annual or bi-annual (when required) approval of an IRB/IEC. The signed IRB/IEC approval letter must identify the documents approved (i.e., list the investigator's name, the protocol number and title, the date of the protocol and informed consent document, and the date of approval of the protocol and the informed consent document). Any advertisements used to recruit patients should also be reviewed by the IRB/IEC. The sponsor will not ship clinical supplies until a signed approval letter from the IRB/ IEC has been received and a Clinical Trial Agreement has been signed by the sponsor and the clinical site.

17.2 Patient Information and Consent

Regulatory agencies have issued regulations to provide protection for human patients in clinical investigations and to describe the general requirements for informed consent.

A copy of the proposed informed consent document should be submitted to the sponsor for review and comment before submission to the IRB/IEC. The study should not begin until the document has been reviewed by the sponsor and must not begin until the document has been approved by the IRB/ IEC. In some instances, the study must not begin until the document has been approved by a regulatory agency. The informed consent document shall contain all of the elements of the informed consent specified in the regulations. Some regulations may require the disclosure of additional information to the patient and/or inclusion of additional information in an informed consent document.

17.3 Patient Confidentiality

All unpublished information that the sponsor gives to the investigator, and all information generated in connection with the study, shall be kept confidential and shall not be disclosed to a third party without the prior written consent of the sponsor or published prior to the sponsor's review in accordance with the terms of the Clinical Trial Agreement. When the sponsor generates reports for presentations to regulatory agencies, one or more of the investigators who have contributed significantly to the study will be asked to endorse the final report. The endorsement is required by some regulatory agencies. The investigator shall not make a patent application based on the results of this study and shall not assist any third party in making such an application without the written authorization of the sponsor.

17.4 Study Committees

17.4.1 Data Monitoring Committee

An independent Data Monitoring Committee (DMC), consisting of 3 to 5 members not associated with the conduct of the study, will be established for this study. The committee will perform data review quarterly and meet at least twice yearly until the final analysis has been performed. Ad-hoc DMC meetings may also be held if a significant issue should arise.

The DMC will be responsible for evaluating the results of safety analyses and will make recommendations to the sponsor. Efficacy data can also be requested, if needed, to evaluate risk/benefit before making a recommendation; however, the trial will not be stopped early for positive efficacy. The DMC will operate under the DMC charter, which specifies the data to be included in each review, rules related to study modification, and protection of the integrity of the data. At each meeting, the DMC will make recommendations to either continue the study unchanged, to modify the study, or to discontinue the study. The DMC will communicate the recommendations to the sponsor. The final decision to act on the DMC recommendations will be made by the sponsor.

17.4.2 Blinded Independent Review Committee

A central blinded Independent Review Committee (BIRC) will evaluate all images collected during the study for the primary endpoint of PFS as well as several secondary endpoints. A BIRC charter defines the procedures used by the committee.

17.4.3 Steering Committee

A steering committee will be constituted with initiation of the study. Its purpose is to function in an advisory capacity to: 1) provide input on study conduct and progress; 2) ensure scientific and ethical integrity of the study; and 3) provide ongoing oversight of safety and efficacy in this open-label study. The steering committee will include clinicians expert in the clinical care and investigation of the targeted patient population, and will also include sponsor representatives. In addition to general study oversight, it will provide input on operational aspects of the study. The committee may make recommendations for the sponsor's consideration based on periodic review.

18 DATA HANDLING AND RECORD KEEPING

18.1 Case Report Forms and Study Records

Study-specific eCRFs will be made available to the investigative site. Study data, contained in source documentation, will be entered into the eCRFs for all patients screened in the study. All pertinent data records are to be submitted to the sponsor during and/or at completion or termination of the study.

18.2 Access to Source Documentation

The investigator agrees that qualified representatives of the sponsor and regulatory agencies will have the right, both during and after this study, to conduct inspections and to audit and review medical records pertinent to the clinical study as permitted by the regulations. Patients will not

be identified by name in any reports stemming from the study, and confidentiality of information in medical records will be preserved. The confidentiality of the patient will be maintained unless disclosure is required by regulations. Accordingly, the following statement (or similar statement) that permits the release of the patient's medical records will be included in the informed consent document:

> *Representatives of regulatory agencies, IRB/IEC, the sponsor, and the patient's personal physician may review the patient medical records and all information related to this study as permitted by law. Patient identity will remain confidential unless disclosure is required by law.*

18.3 Retention of Data

Study documents (including correspondence related to this clinical study, patient records, source documents, eCRFs, study drug inventory records, and IRB/IEC and sponsor correspondence pertaining to the study, original patient, laboratory, and study drug inventory records relating to the study) should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region (that is at least 15 years or at least 2 years have elapsed since the formal discontinuation of clinical development of the product). Study documents should be retained for a longer period if required by applicable regulatory requirements or by agreement with the sponsor. Thereafter, records will not be destroyed without giving the sponsor prior written notice and the opportunity to further store such records, at the sponsor's cost and expense.

18.4 Termination of Study

The sponsor may terminate the study at a study site or in its totality at any time for any of the following reasons:

- Failure to enroll patients
- Protocol violations
- Inaccurate or incomplete data
- Unsafe or unethical practices
- Questionable safety of the study drug
- Suspected lack of efficacy of the study drug; or
- Administrative decision

In the event of the termination of the Study, by either the sponsor or an investigator:

- The investigator will return all study drugs and related study materials to the sponsor.
- A written statement describing why the study was terminated prematurely will be provided by either the sponsor or the investigator.

19 FINANCING AND INSURANCE

A clinical study agreement will be signed by the investigator (and/or, as appropriate, the hospital administrative representative) and the sponsor prior to the start of the study, outlining overall

sponsor and investigator responsibilities in relation to the study. Financial remuneration will cover the cost per included patient, based on the calculated costs of performing the study assessments in accordance with the protocol, and the specified terms of payment will be described in the contract. The contract should describe whether costs for pharmacy, laboratory, and other protocol-required services are being paid directly or indirectly. Prior to the start of the study, investigators and sub-investigators will release sufficient and accurate information that permits the sponsor or sponsor-designated agent to determine that an investigator has no personal or professional financial incentive regarding the future approval or non-approval of the study drug that his/her research might be biased by such financial incentives. The financial information is exclusive of agreements directly related to fees associated with the study being conducted. All information provided will be regarded as strictly confidential and will only be disclosed to the respective regulatory authority.

20 PUBLICATION AND DISCLOSURE POLICY

The investigator must notify the IRB/IEC of the conclusion of the clinical study. This report should be made within 3 months of the completion or termination of the study. The final report sent to the IRB/IEC should also be sent to the sponsor and, along with the completed eCRFs, constitutes the final summary to the sponsor, thereby fulfilling the investigator's regulatory responsibility.

Section 801 of the FDA Amendments Act mandates the registration with ClinicalTrials.gov of certain clinical studies of drugs (including biological products) and medical devices subject to FDA regulations for any disease or condition. The International Committee of Medical Journal Editors (ICMJE) requires study registration as a condition for publication of research results generated by a clinical study (http://www.icmje.org [Accessed: 13 January 2014]). In addition, the EMA requires that clinical studies conducted in the European Union and other countries under their regulatory authority be registered (https://www.clinicaltrialsregister.eu/ [Accessed: 13 January 2014]).

The institution and principal investigator acknowledge that the study is multicenter study, and, as such, agree that they will not publish a publication, abstract, poster or other disclosures ("Publication") before a combined paper that identifies all the sites that participated in the study ("Multi-Center Publication") is published. If the Multicenter Publication has not been completed within one (1) year from the date of the completion, termination, or abandonment of the multicenter study, the institution may publish or present its individual results in accordance with the provisions stated below.

In order to balance the institution's right to publish with ARIAD's proprietary interests, the institution will submit to ARIAD material intended for publication, abstracts, posters, and other disclosures ("Proposed Disclosures") at least 45 days prior to submitting for publication or other disclosure to allow for expeditious review by ARIAD. If ARIAD believes that any Proposed Disclosure contains any information relating to any patentable invention, the disclosure of such Proposed Disclosure shall be delayed for up to sixty (60) days from the date ARIAD receives the Proposed Disclosure to permit ARIAD to file patent applications. If ARIAD believes that any Proposed Disclosure contains Confidential Information, ARIAD shall have the right to require that the institution delete any reference to Confidential Information, excluding the results of the study or other Permitted Research (as defined in Section 11). If the institution and principal

investigator choose not to publish, ARIAD reserves the right to publish the results of the study, and, if appropriate, to include its medical staff in the author list of such publication in accordance with academic publication standards.

Subject to applicable copyright law, if an institution and/or principal investigator publishes results of the study, institution and/or principal investigator hereby grants ARIAD an irrevocable, royalty-free license to make and distribute copies of such publication under any copyright privileges that the institution and/or principal investigator may have.

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22 APPENDICES

APPENDIX A NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (NCI CTCAE)

The United States of America (USA) National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE, v4.0) can be found on the following website.

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40 [Accessed: 15 September 2015]

This version of CTCAE is compatible at the AE (Adverse Event) term level where each CTCAE term is a Medical Dictionary for Regulatory Activities Terminology (MedDRA) LLT (Lowest Level Term). CTCAE v4.0 includes 764 AE terms and 26 'Other, specify' options for reporting text terms not listed in CTCAE. Each AE term is associated with a 5-point severity scale.

APPENDIX B EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

ECOG Performance Status*	Grade
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

*As published in Am J Clin Oncol:

Oken MM, Creech RH, Tormey DC, et al. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

APPENDIX C RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST VERSION 1.1)

Note: These criteria are adapted from Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eu J Cancer 2009;45:228-247.

Choosing Target Lesions

- Select up to 5 lesions (up to 2 per organ)
- Select largest reproducibly measurable lesions
- If the largest lesion cannot be measured reproducibly, select the next largest lesion which can be
- Add up longest diameters (LD) of non-nodal lesions (axial plane)
- Add short axis diameters of nodes
- This is the "sum of the longest diameters" (SLD)

Non-Target Lesions

- All other sites of disease present at baseline and not classified as target lesions will be classified as non-target lesions, including any measurable lesions that were not chosen as target lesions
- It is possible to record multiple non-target lesions involving the same organ as a single item on the eCRF (e.g., "multiple enlarged pelvic lymph nodes")

Determining Response

- Assess at baseline and on study with consistent modalities (CT, MRI, PET/CT)
  - Measure target lesions and calculate SLD
  - Visually assess non-target lesions
  - Search for new lesions
  - Combine these assessments into the overall response

Target Lesion Response

Complete Response (CR)	• Disappearance of all extranodal target lesions. • All pathological lymph nodes must have decreased to <10 mm in short axis
Partial Response (PR)	• At least a 30% decrease in the SLD of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	• SLD increased by at least 20% from the smallest value on study (including baseline, if that is the smallest) • The SLD must also demonstrate an absolute increase of at least 5 mm. (Two lesions increasing from 2 mm to 3 mm, for example, does not qualify)
Stable Disease (SD)	• Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Non-evaluable (NE)	• One or more lesions cannot be evaluated due to missing data or poor image quality unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response (e.g., PD based on other findings)

Non-Target Lesion Response

Complete Response (CR)	• Disappearance of all extranodal non-target lesions • All lymph nodes must be non-pathological in size (<10 mm short axis) • Normalization of tumor marker level
Non-CR/Non-PD	• Persistence of one or more non-target lesions(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	• Unequivocal progression of existing non-target lesions. (Subjective judgment by experienced reader)
Unable to Evaluate (UE)	• One or more lesions cannot be evaluated due to missing data or poor image quality unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response (e.g., PD based on other findings)

New Lesions

• Should be unequivocal and not attributable to differences in scanning technique or findings which may not be a tumor (does not have to meet criteria to be "measurable")

• If a new lesion is equivocal, continue to next time point. If confirmed then, PD is assessed at the date when the lesion was first seen.

• Lesions identified in anatomic locations not scanned at baseline are considered new

• New lesions on ultrasound should be confirmed on CT or MRI

Evaluation of Overall Time Point Response for Patients with Measurable Disease at Baseline

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

NE=Not Evaluable

APPENDIX D DRUGS THAT INTERACT WITH CYP450 ENZYMES

The list of drugs that interact with CYP450 enzymes (notably, CYP2C8 and CYP3A4, 5, and 7) can be found online at http://medicine.iupui.edu/clinpharm/ddis/table.aspx [Accessed: 15 September 2015]. Drugs listed should be avoided if possible.

Note: The website should be used as a guideline and is not necessarily comprehensive. It is the investigator's responsibility to ensure that any drugs under consideration have not been newly identified as CYP inhibitors.

APPENDIX E DRUGS WITH A RISK OF TORSADES DE POINTES

The website http://www.crediblemeds.org/everyone/composite-list-all-qtdrugs/ [Accessed: 10 August 2016] lists four categories of QT-prolonging drugs and may be used as a guide for this protocol. Categories include "Drugs with Known TdP Risk," "Drugs with Possible TdP Risk," "Drugs with Conditional TdP Risk," and "Drugs to be Avoided by Congenital Long QT Patients." The investigator site should register (under the "For Healthcare Providers" tab) to access these categories. If the investigator site does not wish to register, a composite list, including all categories, is available.

Drugs with a known risk of Torsades de Pointes are listed in the table below, and are the only category of QT-prolonging drugs that are prohibited in this study.

Note: The website and table are only to be used as a guideline and are not comprehensive. It is the investigator's responsibility to ensure that any drugs under consideration have not been newly identified as causing Torsades de Pointes.

Drugs Generally Accepted by the CredibleMeds® QTDrug List Advisory Board to have a Known Risk of Causing Torsades de Pointes; Prohibited in this Study

Generic Name	Brand Name (Partial List)	Class/Clinical Use
Amiodarone	Cordarone®, Pacerone®, Nexterone®	Antiarrhythmic / abnormal heart rhythm
Anagrelide	Agrylin®, Xagrid®	Phosphodiesterase 3 inhibitor / thrombocythemia
Arsenic trioxide	Trisenox®	Anticancer / cancer (leukemia)
Astemizole	Hismanal®	Antihistamine / Allergic rhinitis
Azithromycin	Zithromax®, Zmax®	Antibiotic / bacterial infection
Bepridil	Vascor®	Antianginal / angina pectoris (heart pain)
Chloroquine	Aralen®	Antimalarial / malaria
Chlorpromazine	Thorazine®, Largactil®, Megaphen®	Antipsychotic/ Antiemetic / schizophrenia, nausea, many others
Cilostazol	Pletal®	Phosphodiesterase 3 inhibitor/ intermittent claudication
Ciprofloxacin	Cipro®, Cipro-XR®, Neofloxin®	Antibiotic / bacterial infection
Cisapride	Propulsid®	GI stimulant / increase GI motility
Citalopram	Celexa®, Cipramil®	Antidepressant, SSRI / depression
Clarithromycin	Biaxin®, Prevpac®	Antibiotic / bacterial infection

Generic Name	Brand Name (Partial List)	Class/Clinical Use
Cocaine	Cocaine	Local anesthetic / anesthesia (topical)
Disopyramide	Norpace®	Antiarrhythmic / abnormal heart rhythm
Dofetilide	Tikosyn®	Antiarrhythmic / abnormal heart rhythm
Domperidone	Motilium®, Motillium®, Motinorm Costi®, Nomit®	Antinausea / nausea, vomiting
Donepezil	Aricept®	Cholinesterase inhibitor/dementia (Alzheimer's Disease)
Dronedarone	Multaq®	Antiarrhythmic / abnormal heart rhythm
Droperidol	Inapsine®, Droleptan®, Dridol®, Xomolix®	Antipsychotic / Antiemetic / anesthesia (adjunct), nausea
Erythromycin	E.E.S.®, Robimycin®, EMycin®, Erymax®, Ery-Tab®, Eryc Ranbaxy®, Erypar®, Eryped®, Erythrocin Stearate Filmtab®, Erythrocot®, E-Base®, Erythroped®, Ilosone®, MY-E®, Pediamycin®, Zineryt®, Abboticin®, Abboticin-ES®, Erycin®, PCE Dispertab®, Stiemycine®, Acnasol®, Tiloryth®	Antibiotic / bacterial infection, increase GI motility
Escitalopram	Cipralex®, Lexapro®, Nexito®, Anxiset-E®, Exodus®, Esto®, Seroplex®, Elicea®, Lexamil®, Lexam®, Entact®, Losita®, Reposil®, Animaxen®, Esitalo®, Lexamil®	Antidepressant, SSRI / depression (major), anxiety disorders
Flecainide	Tambocor®, Almarytm®, Apocard®, Ecrinal®, Flécaine®	Antiarrhythmic / abnormal heart rhythm
Fluconazole	Diflucan®, Trican®	Antifungal / Fungal infection
Gatifloxacin	Tequin®	Antibiotic / bacterial infection
Grepafloxacin	Raxar®	Antibiotic / bacterial infection
Halofantrine	Halfan®	Antimalarial / malaria

Generic Name	Brand Name (Partial List)	Class/Clinical Use
Haloperidol	Haldol®, Aloperidin®, Bioperidolo®, Brotopon®, Dozic®, Duraperidol®, Einalon S®, Eukystol®, Halosten®, Keselan®, Linton®, Peluces®, Serenace®, Serenase®, Sigaperidol®	Antipsychotic / schizophrenia, agitation
Ibutilide	Corvert®	Antiarrhythmic / abnormal heart rhythm
Levofloxacin	Levaquin®, Tavanic®	Antibiotic / bacterial infection
Levomepromazine	Nosinan®, Nozinan®, Levoprome®	Antipsychotic / schizophrenia
Levomethadyl acetate	Orlaam®	Opioid agonist / narcotic dependence
Mesoridazine	Serentil®	Antipsychotic / schizophrenia
Methadone	Dolophine®, Symoron®, Amidone®, Methadose®, Physeptone®, Heptadone®	Opioid agonist / narcotic dependence, pain
Moxifloxacin	Avelox®, Avalox®, Avelon®	Antibiotic / bacterial infection
Ondansetron	Zofran®, Anset®, Ondemet®, Zuplenz®, Emetron®, Ondavell®, Emeset®, Ondisolv®, Setronax®	Antiemetic / nausea, vomiting
Oxaliplatin	Eloxatin®	Antineoplastic agent / cancer
Papaverine HCl	None	Vasodilator, coronary / diagnostic adjunct
Pentamidine	Pentam®	Antifungal / fungal infection (Pneumocystis pneumonia)
Pimozide	Orap®	Antipsychotic / Tourette's Disorder
Probucol	Lorelco®	Antilipemic / Hypercholesterolemia
Procainamide	Pronestyl®, Procan®	Antiarrhythmic / abnormal heart rhythm
Propofol	Diprivan®, Propoven®	Anesthetic, general / Anesthesia
Quinidine	Quinaglute®, Duraquin®, Quinact®, Quinidex®, Cin-Quin®, Quinora®	Antiarrhythmic / abnormal heart rhythm

Generic Name	Brand Name (Partial List)	Class/Clinical Use
Roxithromycin	Rulide®, Xthrocin®, Roxl-150®, Roxo®, Surlid®, Rulide®, Biaxsig®, Roxar®, Roximycinv®, Roxomycin®, Rulid®, Tirabicin®, Coroxin®	Antibiotic / bacterial infection
Sevoflurane	Ulane®, Sojourn®	Anesthetic, general / anesthesia
Sotalol	Betapace®, Sotalex®, Sotacor®	Antiarrhythmic / abnormal heart rhythm
Sparfloxacin	Zagam®	Antibiotic / bacterial infection
Sulpiride	Dogmatil®, Dolmatil®, Eglonyl®, Espiride®, Modal®, Sulpor®	Anti-psychotic, atypical / schizophrenia
Sultopride	Barnetil®, Barnotil®, Topral®	Antipsychotic, atypical / schizophrenia
Terfenadine	Seldane®	Antihistamine / allergic rhinitis
Thioridazine	Mellaril®, Novoridazine®, Thioril®	Antipsychotic / schizophrenia
Vandetanib	Caprelsa®	Anticancer / cancer (thyroid)

APPENDIX F PROTOCOL HISTORY

PROTOCOL REVISION HISTORY:

Amendment Number	Protocol Version Number	Date
Original Protocol	Version 1.0	22 October 2015
Amendment 01	Version 2.0	21 September 2016
Amendment 02	Version 3.0	17 May 2018
Amendment 03	Version 4.0	12 May 2020

Amendment #2, Protocol Version 3.0

The primary sections of the protocol affected by the changes in Amendment 2 are indicated. The corresponding text has been revised throughout the protocol.

Change #1. Removed the exception for hormonal contraception from the list of prohibited concurrent medications and procedures; hormonal contraception is no longer allowed

The primary change occurs in Section 13.3 Prohibited Treatment(s) Therapy:

Deleted text: "Any other systemic anticancer therapy including, but not limited to: chemotherapeutic agents, immunotherapy, biological response modifiers (excluding growth factors), radiotherapy, and/or systemic hormonal therapy (**with the exception of** local therapies, such as SRS, used for palliative or symptomatic control of existing lesions, with appropriate treatment interruption at the discretion of the investigator). ~~Hormonal contraception is allowed~~.

Rationale for change: Brigatinib induces CYP3A in vitro and may decrease concentrations of CYP3A substrates, including hormonal contraceptives. Coadministration of brigatinib with hormonal contraceptives can result in decreased concentrations and loss of efficacy of hormonal contraceptives.

Section 4 Protocol Synopsis also contains this change.

Change #2: Removed all forms of hormonal contraception from the list of highly effective contraception methods.

The primary change occurs in Section 14.3.113.3 Pregnancy and Breastfeeding.

Deleted text:

- ~~combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:~~
  - ~~oral~~
  - ~~intravaginal~~
  - ~~transdermal~~
- ~~progestogen-only hormonal contraception associated with inhibition of ovulation:~~

- ~~oral~~
- ~~injectable~~
- ~~implantable~~

- ~~intrauterine hormone-releasing system (IUS)~~

Rationale for change: Brigatinib induces CYP3A in vitro and may decrease concentrations of CYP3A substrates, including hormonal contraceptives. Coadministration of brigatinib with hormonal contraceptives can result in decreased concentrations and loss of efficacy of hormonal contraceptives.

Change #3: Added new protocol deviation language.

The primary change occurs in Section 15.9 Protocol Deviations/Violations:

Added text: The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated, it will be reported to regulatory authorities as a serious breach of GCP and the protocol.

Rationale for Change: Additional protocol deviation language was added per the sponsor's updated template.

Amendment #1, Protocol Version 2.0

REASON FOR AMENDMENT:

The amendment serves the following purposes:

1. Added EORTC QLQ-LC13 quality of life assessment
2. Amended the required duration for contraceptive use after end of treatment with crizotinib
3. Added the definition of highly effective contraception to be used during and after the study

4. Amended wording regarding possible additional drug-drug interactions with crizotinib and the possibility that the effectiveness of oral contraceptives may be reduced while taking crizotinib
5. Amended the recommendations and requirements for monitoring of vision dysfunction during treatment with brigatinib and crizotinib and management of visual loss during treatment with crizotinib and visual disturbance during treatment with brigatinib
6. Clarified that patients will continue to receive study drug until discontinuation
7. Clarified the timing of study procedures:
    a. that imaging by computed tomography (CT) or magnetic resonance imaging (MRI) should continue until the end of treatment, rather than disease progression, as some patients may remain on treatment after progressive disease (PD)
    b. that additional pregnancy testing should be performed if recommended or required per local guidelines or regulations
8. Clarified inclusion criterion #1, that patients with **locally advanced or recurrent** Stage IIIB non-small cell lung cancer (NSCLC) may be included in the study
9. Modified inclusion criterion #5 to specify that >grade 1 alopecia or peripheral neuropathy related to prior anticancer therapy are allowed if deemed irreversible
10. Clarified that baseline laboratory tests that need to be repeated on Cycle 1 Day 1 (because screening laboratory tests were performed >7 days prior to the first dose) should be obtained before starting treatment
11. Clarified administrative information and processes:
    a. the process for investigator reporting of serious adverse events (SAEs)
    b. the process regarding review and approval of protocol amendments
    c. amended the sponsor contact and signatory information
12. Corrected some typographical and grammatical errors and inconsistencies throughout the protocol
13. Updated Appendix E (Drugs with a Risk of Torsades de Pointes) to be based on a more recent list provided by CredibleMeds® (dated 10 August 2016)

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	13-May-2020 12:47 UTC
	Clinical Approval	13-May-2020 13:16 UTC
	Clinical Approval	13-May-2020 13:29 UTC