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

NCT Number: NCT02094573

Protocol Approve Date: 24 August 2015

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

- Named persons or organizations associated with the study.
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- 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 Randomized Phase 2 Study of AP26113 in Patients with ALK-positive, Non-small Cell Lung Cancer (NSCLC) Previously Treated with Crizotinib
Protocol Number:	AP26113-13-201
Study Phase:	Phase 2
Product Name:	AP26113
IND Reference Number:	IND 110,935
EudraCT Number:	2013-002134-21
Sponsor:	ARIAD Pharmaceuticals, Inc. 26 Landsdowne Street Cambridge, MA 02139-4234 Telephone: +1 (617) 494-0400
Protocol Issue Date:	24 August 2015
Version Number:	Version 4.0 (South Korea only)

PROTOCOL REVISION HISTORY:

Amendment Number	Protocol Version Number	Date
Original Protocol	Version 1.0	27 June 2013
Amendment 1	Version 2.0	3 February 2014
Amendment 2	Version 3.0	29 July 2014
Amendment 3	Version 4.0 (South Korea only)	24 August 2015

2 SIGNATURE PAGES

2.1 Signatory*

PPD

*The protocol will be approved electronically in ARIAD Pharmaceutical Inc.'s Electronic Document Management System (FirstDoc). A copy of the eSignature will be included with the final document.

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)

_____

Investigator's Name (print)

2.3 Sponsor Representative Signature

ARIAD Pharmaceuticals, Inc. has approved of this protocol and assures that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality.

Sponsor Representative's Signature

PPD

Date (dd-mmm-yyyy)

3 CONTACT INFORMATION

Sponsor	ARIAD Pharmaceuticals, Inc. 26 Landsdowne Street Cambridge, MA 02139-4234 USA Telephone: +1 (617) 494-0400
Sponsor Medical Monitor:	PPD
Sponsor Additional Contact:	PPD

4 PROTOCOL SYNOPSIS

Sponsor	ARIAD Pharmaceuticals, Inc. 26 Landsdowne Street Cambridge, MA 02139-4234
Study Treatment	AP26113
Protocol Title	A Randomized Phase 2 Study of AP26113 in Patients with ALK-positive, Non-small Cell Lung Cancer (NSCLC) Previously Treated with Crizotinib
Development Phase	Phase 2
Summary and Study Rationale	AP26113 is a novel, synthetic, orally-active tyrosine kinase inhibitor (TKI) discovered and developed at ARIAD Pharmaceuticals, Inc. (ARIAD, the sponsor). A primary target of AP26113 is anaplastic lymphoma kinase (ALK). Activating gene rearrangements in ALK-positive (ALK+) tumors have been identified as driver mutations in patients with non-small cell lung cancer (NSCLC) and other cancers. Activating gene rearrangements in ALK have been identified as driver mutations in approximately 3% to 5% of patients with NSCLC (Perner et al, 2008; Wong et al, 2009). Crizotinib (XALKORI®, Pfizer, Inc.) has demonstrated clinical efficacy in ALK+ NSCLC (Kwak et al., 2010). 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®, Pfizer, Inc.). These two studies served as the basis for crizotinib's accelerated approval for treatment of ALK+ advanced NSCLC in the United States and conditional approval in the European Union. Although crizotinib is an effective treatment of ALK+ NSCLC, a substantial proportion (50% and 39%, respectively) of ALK+ NSCLC patients in the pivotal trials that supported its accelerated approval failed to achieve a response. For those patients who did respond, the benefit was relatively short-lived with a median duration of response ranging from 42 to 48 weeks (XALKORI®, Pfizer, Inc.). In many patients, loss of response manifests as systemic progression, but in some patients the disease progresses only within the brain, possibly as a result of low 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 clearer (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, and L1152R, G1269A, S1206Y, F1174L, D1203N, C1156Y, T1151Tins, and G1202R mutations) may act by reducing the binding affinity of crizotinib to ALK (Bang, 2012). Other mechanisms of secondary resistance to crizotinib include the amplification of the ALK fusion gene, exploiting crizotinib's suboptimal potency against ALK and the activation of alternate signaling pathways (Camidge et al, 2012; Katayama et al, 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 retains activity against all key crizotinib-resistance mutations and that can also achieve deep and prolonged target inhibition both systemically and in the CNS.

AP26113 has demonstrated potent inhibitory activity against activated ALK (8-fold more potent than crizotinib) and pan-inhibitory activity against all 9 clinically identified crizotinib-resistant mutants identified to date.

Based on favorable preclinical in vitro and in vivo pharmacology and toxicology studies, a phase 1/2 clinical study of AP26113 (study AP26113-11-101) was initiated on 20 September 2011. Study 101 consists of a phase 1 dose escalation portion, followed by a phase 2 expansion portion with defined clinical cohorts. The trial is still enrolling patients.

As of 6 September 2013, 91 patients were treated with AP26113 at doses ranging from 30 mg QD to 300 mg QD, including 45 patients treated at 180 mg QD. Of these, the median age was 57 years and 60% were female. The majority (82%) of patients were diagnosed with adenocarcinoma of the lung (NSCLC). Forty-two (46%) patients had a history of ALK rearrangement. Approximately half (51%) of patients had received one or two prior systemic treatment regimens while 24% received more than 2 prior systemic treatment regimens.

In the phase 1 dose-escalation portion of the study, patients were administered AP26113 at doses ranging from 30 mg once-daily (QD) to 300 mg QD. Twice-daily (BID) dose regimens were also evaluated in some patients during dose-escalation. At doses of 90 mg and higher, mean plasma steady-state trough drug concentrations that exceeded levels predicted preclinically to inhibit crizotinib-resistant ALK mutants were achieved. No dose-limiting toxicities (DLTs) were observed in the phase 1 portion at doses up to 180 mg QD. At higher doses, DLTs of grade 3 alanine aminotransferase (ALT) increased (240 mg QD) and grade 4 dyspnea (300 mg QD) were reported. The maximum tolerated dose (MTD) was not formally determined. However, based on these results, the dose of 180 mg QD was initially chosen as the RP2D for the phase 2 expansion portion of the study.

In the phase 2 expansion portion of the study, 3 of 26 (12%) patients treated with 180 mg QD experienced early onset pulmonary symptoms that in some cases constituted pneumonitis (described in more detail below and in Section 7.3). Consequently, two additional RP2Ds were tested: 90 mg QD and a 7-day dosing period of 90 mg QD followed by escalation to 180 mg QD. Preliminary data (as described below and in Section 7.3) support testing these regimens further in this randomized trial.

Among all enrolled patients (as of 6 September 2013), the most common treatment-emergent AEs (≥10% of patients) were nausea (38.5%), fatigue (34.1%), diarrhea (31.9%), cough (20.9%), headache (19.8%), dyspnea (16.5%), vomiting (16.5%), amylase increased (12.1%), decreased appetite (12.1%), and muscle spasms (11.0%). Treatment-related AEs of grade ≥3 occurring in 2 or more patients included dyspnea (4%), fatigue (3%), diarrhea (2%), hypoxia (2%), and pneumonitis (2%). Serious adverse events (SAEs) (treatment-related) occurring in 2 or more patients were dyspnea (7%), pneumonia (4%), hypoxia (2%), and pneumonitis (2%).

The early onset pulmonary events that occurred immediately following initiation of treatment included dyspnea, hypoxia, pneumonia, ground glass and interstitial chest CT findings, and pneumonitis, and were moderate or severe. The early onset pulmonary events are dose-related and not observed at 90 mg. Symptoms typically occur within 48 hours of initial dosing. Symptoms have recurred in some patients upon rechallenge; however, many patients were able to continue therapy, even at

	higher doses, with optimal management. In the phase 2 expansion portion of study 101, early onset pulmonary events were observed in 3 out of 26 patients dosed at 180 mg QD. In the study overall, there were 6 cases (13%) of an early onset pulmonary syndrome in 45 patients dosed at 180 mg QD, and 4 additional cases observed at higher doses (2 at 240 mg QD and 2 at 300 mg QD) that comprise a total of 10 cases (15%) in 59 patients treated with 180 mg QD or higher doses of AP26113 in the study. All 10 were SAEs. As of 6 September 2013, 21 patients have been enrolled in the 101 study utilizing the 90 mg to 180 mg regimen. No cases of early onset pulmonary AEs have been observed using this regimen. Antitumor activity has been observed in patients with crizotinib-resistant ALK+ NSCLC as well as in TKI-naïve patients. Overall, of the 34 ALK+ NSCLC patients treated with AP26113 who have been imaged, 22 responded (65% ORR; 95% CI: 47%-80%). In ALK+ NSCLC patients treated with prior crizotinib (and no other ALK TKIs), responses were documented in 19 out of 28 patients (68% ORR; 95% CI: 48%-84%). An ORR of 100% was observed for TKI-naïve patients (3/3), including one complete response. Response duration ranged from 8+ to 40+ weeks in 14 patients with confirmed responses. In addition, 8 of 10 ALK+ NSCLC patients with active CNS lesions at baseline had evidence of radiographic improvement in the CNS (duration of CNS benefit in these patients ranged from 8+ to 40+ weeks). Responses in CNS lesions were observed in patients receiving 180 mg QD or higher. Based on observations made from the phase 1/2 study, two RP2Ds are recommended for further study. There is support for testing 90 mg QD, as this dose appears to have an acceptable safety profile and is productive of responses. But there is reason for utilizing higher doses as well, particularly with regard to CNS penetration and activity in this sanctuary site. The addition of a 90-mg QD 7-day lead-in to therapy with 180 mg QD appears to lessen the incidence of early pneumonitis and pulmonary symptoms. Therefore, this dose will be tested as a RP2D as well as the 90-mg QD regimen. In summary, AP26113 was generally safe at doses up to 180 mg QD in the phase 1/2 trial. AP26113 exhibited substantial anticancer activity in patients with crizotinib-resistant ALK+ NSCLC. AP26113 is active in ALK+ brain metastases with frequent responses of clinically meaningful duration. In this trial, patients with ALK+ NSCLC who have experienced failure of crizotinib therapy will be randomized 1:1 to receive either 90 mg QD continuously (in Arm A) or a lead-in dose of 90 mg QD for 7 days followed by 180 mg QD continuously (in Arm B).
Study Design	Phase 2, open-label, randomized, multicenter, international study.
Study Objectives	The primary objective of the study is to determine the efficacy of AP26113, as evidenced by objective response rate, in patients with ALK-positive locally advanced or metastatic NSCLC whose disease has progressed on therapy with crizotinib. Two dosing regimens will be tested. The secondary objectives of the study (for each dosing regimen) are: 1. To further characterize the efficacy of AP26113 in patients with ALK-positive, locally advanced or metastatic NSCLC whose disease has progressed on therapy with crizotinib, as shown by disease control rate, time to/duration of response, progression-free survival (PFS), overall survival (OS), and time on treatment 2. To assess CNS response and PFS, per RECIST v1.1, in those patients who have active brain metastases 3. To assess the safety and tolerability of AP26113 in study patients

	4. To measure steady-state plasma levels of AP26113 for use in 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) CCI [redacted]
Study Endpoints	Primary Endpoint: Confirmed Objective Response Rate (ORR), as assessed by the investigator, per RECIST v1.1 Secondary Endpoints: 1. Confirmed ORR, as assessed by a central independent review committee (IRC), per RECIST v1.1 2. CNS response (ORR and PFS, per RECIST v1.1, in patients who have active brain metastases) 3. Time to response 4. Duration of response 5. Time on treatment 6. Disease control rate (the percentage of patients with best response of complete response [CR], PR, or SD), per RECIST v1.1 7. Progression Free Survival (PFS) 8. Overall Survival (OS) 9. Safety and tolerability 10. Steady-state plasma level of AP26113 for use in population PK modeling 11. Patient-reported symptoms of lung cancer and HRQoL scores, assessed with CCI [redacted]
Inclusion Criteria	All patients must meet all the following eligibility criteria for study entry: 1. Have histologically or cytologically confirmed locally advanced or metastatic NSCLC that is ALK+. 2. Must meet one of the following two criteria: a. Have documented ALK rearrangement by a positive result from the Vysis® ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit; or b. Have documented ALK positivity by a different test and tissue available for the Vysis® FISH test. Tissue should be derived preferably from a

biopsy taken after progression with crizotinib. If such a sample is not available, testing may be performed with archived tumor tissue.

3. Had progressive disease while on crizotinib, as assessed by the investigator or treating physician.
4. No longer a required criterion as of Amendment 2.
5. Have at least 1 measurable lesion per RECIST v1.1 (see Appendix C). Note: Previously irradiated lesions may not be used for target lesions, unless there is unambiguous radiological progression after radiotherapy. Brain lesions may not be used as target lesions if they were: 1) previously treated with whole brain radiation therapy (WBRT) within 3 months, or 2) previously treated by stereotactic radiosurgery (SRS) or surgical resection.
6. No longer a required criterion as of Amendment 2.
7. Recovered from toxicities related to prior anticancer therapy to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, v4.0) grade ≤2 (see Appendix A).
8. Are a male or female patient ≥18 years old.
9. Have a life expectancy ≥3 months.
10. Have adequate organ and hematologic function, as determined by:
    a. Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤2.5 x upper limit of normal (ULN; ≤5 x ULN is acceptable if liver metastases are present)
    b. Total serum bilirubin ≤1.5 x ULN (<3.0 x ULN for patients with Gilbert syndrome)
    c. Serum creatinine ≤1.5 x ULN
    d. Serum lipase/amylase ≤1.5 x ULN
    e. Absolute neutrophil count (ANC) ≥1500/µL
    f. Platelets ≥75000/µL
    g. Hemoglobin ≥10 g/dL
11. Have Eastern Cooperative Oncology Group (ECOG) performance status ≤2 (see Appendix B).
12. Have normal QT interval on screening electrocardiogram (ECG) evaluation, defined as QT interval corrected (Fridericia) (QTcF) of ≤450 ms in males or ≤470 ms in females.
13. For female patients of childbearing potential, a negative pregnancy test must be documented prior to enrollment.
14. Female and male patients who are fertile must agree to use a highly effective form of contraception with their sexual partners throughout study participation.
15. Must provide a 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.
16. Have the willingness and ability to comply with scheduled visits and study procedures.

Exclusion Criteria	Patients meeting any of the criteria below are ineligible for the study: 1. Received any prior ALK-targeted TKI other than crizotinib. 2. Received crizotinib within 3 days of the first dose of AP26113 (Day 1, Cycle 1). 3. Received cytotoxic chemotherapy, investigational agents, or radiation within 14 days, except SRS or stereotactic body radiosurgery. 4. Received monoclonal antibodies or had major surgery within 30 days of the first dose of AP26113 (Day 1, Cycle 1). 5. Have been diagnosed with another primary malignancy within the past 3 years (except for adequately treated non-melanoma skin cancer, cervical cancer in situ, or prostate cancer, which are allowed within 3 years). 6. Have symptomatic CNS metastases that are neurologically unstable or require an increasing dose of corticosteroids. 7. Have current spinal cord compression. 8. 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 AP26113 b. Unstable angina within 6 months prior to first dose c. Congestive heart failure (CHF) within 6 months prior to first dose d. History of clinically significant (as determined by the treating physician) atrial arrhythmia e. Any history of ventricular arrhythmia f. Cerebrovascular accident or transient ischemic attack within 6 months prior to first dose 9. Have a history or the presence of pulmonary interstitial disease or drug-related pneumonitis. 10. Have an ongoing or active infection. The requirement for intravenous (IV) antibiotics is considered active infection. 11. Have a known history of human immunodeficiency virus (HIV). Testing is not required in the absence of history. 12. Have a history of or active significant gastrointestinal (GI) bleeding within 3 months of the first dose of AP26113. 13. Have a known or suspected hypersensitivity to AP26113 or its excipients. 14. Have malabsorption syndrome or other GI illness that could affect oral absorption of the study drug. 15. Have any condition or illness that, in the opinion of the investigator, would compromise patient safety or interfere with evaluation of the study drug. 16. Be pregnant or breastfeeding.
Approximate Number of Patients	Approximately 218 patients total (109 on each dosing regimen)
Approximate Duration of	Patients will continue to be dosed with AP26113 until they experience disease

Patient Participation	progression or intolerable toxicity. Treatment may be continued after progression, at the discretion of the investigator. On Arm A, at the time of progression, the patient may continue at the same dose or the patient's dose may be escalated from 90 mg QD to 180 mg QD. For patients on either arm receiving 180 mg QD, at the time of progression, treatment may continue if there is still evidence of clinical benefit (see Section 13.1.2 for details on treatment continuation after progression). Follow-up assessments (ie, contacting the patient for survival and subsequent anticancer therapy) must be performed every 3 months after the End-of-Treatment. Follow-up will continue for 2 years after the last patient enrolls into the study.
Approximate Duration of Study	The total estimated duration of the study is at least 3 years, including approximately 18 months to accrue patients, with 2 years for treatment and follow-up for the last patient. Patients will be allowed to receive study drug beyond this period until disease progression or they discontinue treatment for other reasons.
Approximate Number of Study Centers	Approximately 100 centers
Study Drug Administration and Modification	Patients will be randomized 1:1 to receive AP26113 in one of two different dosing regimens. Arm A: AP26113 will be administered at a dose of 90 mg QD, continuously. Arm B: AP26113 will be administered at a dose of 90 mg QD for 7 days, then 180 mg QD, continuously. A cycle of therapy will comprise 28 days of treatment, regardless of dose. Patients will take the prescribed dose with water (recommended 240 mL). Dose interruptions or reductions should be implemented for patients who experience treatment-related adverse events, upon clinical judgment of the investigator. Guidelines for continued treatment after disease progression are discussed in Section 13.1.2. Re-escalation of doses will occur only in consultation with the sponsor (see Section 13.1.5). Guidelines for management of treatment-related adverse events are described in Section 13.1.4.
Concomitant Treatment	Palliation 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 SRS are allowed to continue study treatment after appropriate interruption, as determined by the investigator with sponsor agreement; however, for analysis purposes, these patients will be considered to have progressive disease. After a patient has begun the study, the addition of the following concurrent medications or procedures are prohibited: • Any other systemic anticancer therapy. • Use of any other investigational drug or device. • 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. • Extensive surgery requiring in-patient care (patients may have an interruption in therapy for 14 days should emergency surgery be required).

	In vitro studies with human liver microsomes indicate that cytochrome 450 (CYP) 2C8 and CYP3A4 are involved in the human metabolism of AP26113. Medications and dietary (grapefruit-containing products) or herbal products (St John's Wort) that are strong inhibitors or inducers of P450 cytochromes, in particular, CYP2C8 or CYP3A4, should be avoided (see Appendix D). AP26113 is not a reversible inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5, with 50% inhibitory concentrations (IC_{50}s) of >70 µM. AP26113 is also not a metabolism-dependent or a time-dependent inhibitor of the CYPs tested. Hence, drug-drug interactions due to inhibition of CYPs by AP26113 are unlikely.
Efficacy Evaluation	Tumor response will be determined per RECIST v.1.1 (see Appendix C) by the investigator, with a secondary independent radiological review. Evaluation of tumor response will be by ORR (confirmed ≥4 weeks after initial response), disease control rate (CR, PR, SD), time to/duration of response, PFS, OS, and time on treatment. CNS response will be evaluated by ORR and PFS.
Safety Evaluation	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). All patients receiving at least 1 dose of AP26113 will be considered evaluable for safety. AE incidence rates, as well as the frequency of occurrence of overall toxicity, categorized by toxicity grades (severity), will be described. Listings of laboratory test results will also be generated, and descriptive statistics summarizing the changes in laboratory tests over time will be presented.
Pharmacokinetic Evaluations	Sparse plasma AP26113 concentration data obtained from this study will be included in integrated population PK analyses, along with data from study AP26113-11-101, with the objective of further characterizing the plasma PK of AP26113 in the intended patient population, and to assess exposure-response (for efficacy) and exposure-safety relationships in patients receiving AP26113.
Exploratory Biomarker Evaluations in Tissue and Plasma	CCI [redacted]
Patient-Reported Symptoms and Quality of Life Evaluations	Patient-reported symptoms and HRQoL will be collected by administering the EORTC QLQ C30 (v3.0) questionnaire, which has been studied extensively, is validated, and is suitable for use in global clinical studies. The questionnaire will be administered to patients in their local language.
Statistical Methods	Descriptive statistics and analyses will be provided. All patients who are randomized to receive one of the two dosing regimens will be included in the primary analysis of efficacy. All patients who receive at least 1 dose of AP26113 will be included in the analysis of safety. This will include patients who have experienced failure of crizotinib but do not have a history of ALK status by Vysis® FISH test regardless of the results of the subsequent test (patients may be treated before such confirmation). A per-protocol analysis will be performed for the primary endpoint and selected

	secondary efficacy endpoints, which excludes patients with no history or confirmation of ALK rearrangement by Vysis® FISH. Each dosing regimen will be summarized separately. No inferential comparisons between the two regimens will be performed. For the primary efficacy test of the primary endpoint, ORR as assessed by the investigator, the overall alpha of 0.05 two-sided will be split in half to adjust for the fact that a test of each regimen will be performed. For each regimen, the primary analysis of the primary endpoint will be performed using a 2-sided exact 97.5% confidence interval. The primary analysis is planned to be conducted when all ongoing patients have completed their Cycle 6 disease assessment. Two-sided exact 95% binominal confidence intervals will be computed for confirmed ORR as assessed by the IRC, CNS ORR, and disease control rate. Kaplan-Meier methods, including medians and confidence intervals, will be used to evaluate PFS, CNS PFS, OS, and duration of response. Descriptive statistics will be used to summarize time to response in responders and time on treatment. HRQoL and patient-reported symptoms will be analyzed using a mixed-effects model for repeated measures to evaluate changes in linearly transformed scores from baseline at each subsequent study visit through the end of the study. Means and medians of questionnaire raw scores will be summarized by time point, overall, and for each scale. Further details of statistical analyses including the data handling rules will be provided in the Statistical Analysis Plan (SAP).
Rationale for Number of Patients	The purpose of this phase 2 study is to determine the ORR of two dosing regimens of oral AP26113 in patients with ALK+ NSCLC whose disease has progressed on therapy with crizotinib. A sample size of at least 109 patients in each treatment group will allow the study to have an approximate 90% power to rule out an uninteresting rate of 20% when the true rate is 35% or higher with alpha=0.025 two-sided.

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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
ASCO	American Society of Clinical Oncology
AUC	area under the curve
β-HCG	beta-human chorionic gonadotropin
BAL	bronchoalveolar lavage
BNP	B-type natriuretic peptide
BUN	blood urea nitrogen
CBC	complete blood count
CHF	congestive heart failure
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum plasma concentration
CNS	central nervous system
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events (version 4.0)
CYP	cytochrome P450
DDI	drug-drug interaction
DLCO	diffusing capacity of the lung for carbon monoxide
DLT	dose-limiting toxicity
EC	Ethics Committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EML4	echinoderm mictrotubule-associated protein-like 4
EORTC	European Organisation for Research and Treatment of Cancer
FDA	Food and Drug Administration (United States)
FFPE	formalin-fixed, paraffin-embedded
GCP	Good Clinical Practice
GI	gastrointestinal
HIV	human immunodeficiency virus
HRQoL	health-related quality-of-life
IC_{50}	50% maximum inhibitory concentration
ICMJE	International Committee of Medical Journal Editors
IHC	immunohistochemistry
IGF-1R	insulin-like growth factor 1 receptor

Abbreviation	Term
INR	International Normalized Ratio
IRB	Institutional Review Board
IRC	independent review committee
IV	intravenous
LD_{50}	oral lethal dose
MI	myocardial infarction
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute (of the United States)
NSCLC	non-small cell lung cancer
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 outcomes
PT	prothrombin time
PTT	partial thromboplastin time
QD	once-daily
QLQ	Quality of Life Questionnaire
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)
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SRS	stereotactic radiosurgery
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
US	United States
WBRT	whole brain radiation therapy

6 DEFINITIONS OF TERMS

Term	Definition
30 Days After Last Dose	At *30 days after last dose* of AP26113, 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.
End-of-Treatment	*End-of-treatment* occurs when a patient receives final dose of study drug or discontinues taking study drug and completes the *end-of-treatment* assessments.
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 received study drug.
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 a patient begins after the last completed site visit 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 the first dose of study drug is administered.
Sponsor	Throughout this document, the term *sponsor* refers to all applicable departments within ARIAD Pharmaceuticals, Inc., 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, the *study drug* is AP26113.
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.

7 INTRODUCTION

7.1 Background

AP26113 is a novel, synthetic, orally-active tyrosine kinase inhibitor (TKI) discovered and developed at ARIAD Pharmaceuticals, Inc. (ARIAD, the sponsor). A primary target of AP26113 is anaplastic lymphoma kinase (ALK). Activating gene rearrangements in ALK-positive (ALK+) tumors have been identified as driver mutations in patients with non-small cell lung cancer (NSCLC) and other cancers.

ALK is a tyrosine kinase encoded on chromosome 2 that is primarily involved in developmental processes and expressed at low levels in adults (Camidge et al, 2012). The first genetic rearrangement of ALK seen in NSCLC involved a fusion between the echinoderm mictrotubule-associated protein-like 4 (EML4) gene and the ALK tyrosine kinase domain. EML4-ALK had the capacity to transform fibroblasts grown in culture and as subcutaneous xenografts (Suda et al, 2007). Since then, a number of additional ALK fusion partners have been described in NSCLC, such as tyrosine receptor kinase-fused gene (Rikova et al, 2007) and kinesin family member 5B (Takeuchi et al, 2009), all of which are believed to result in aberrant ALK signaling and oncogenic transformation. Aberrant ALK, including ALK rearrangements, can potentially act as an oncogene in several different cancers, especially NSCLC (Camidge et al, 2012).

The frequency of ALK rearrangements in the overall population of NSCLC patients ranges from 3% to 5%, which represents approximately 8,000 patients in the United States (US) each year and approximately 40,000 patients worldwide each year (Perner et al, 2008; Wong et al, 2009). ALK rearrangements are more common among patients with adenocarcinoma histology, patients who have never smoked, and patients who have wild-type epidermal growth factor receptor (EGFR) and v-Ki-ras2 Kirsten RAt Sarcoma viral oncogene homolog (Camidge et al, 2010).

Crizotinib (XALKORI®, Pfizer, Inc.) has demonstrated clinical efficacy in ALK+ NSCLC (Kwak et al, 2010). In a phase 1 study of crizotinib that included 119 ALK+ NSCLC patients who were assessable for response, the objective response rate (ORR) was 61% and the median progression-free survival (PFS) was 48 weeks (XALKORI®, Pfizer, Inc.). In a phase 2 single-arm study of crizotinib that included 136 patients with ALK-positive tumors (PROFILE 1005), the ORR was 50% and the median duration of response was 42 weeks (XALKORI®, Pfizer, Inc.). These two studies served as the basis for crizotinib's accelerated approval by the Food and Drug Administration (FDA) in the US and conditional approval by the European Medicines Agency (EMA) in the European Union. The clinical benefit of treatment with crizotinib in ALK+ NSCLC patients (ie, improvement in disease-related symptoms or overall survival) has not yet been confirmed but additional randomized studies are ongoing. Currently, crizotinib is the only ALK inhibitor that has obtained regulatory approval.

Although crizotinib is an effective treatment of ALK+ NSCLC, a substantial proportion (50% and 39%, respectively) of ALK+ NSCLC patients in the pivotal studies that supported its accelerated approval failed to achieve a response. For those patients who did respond, the benefit was relatively short-lived with a median duration of response ranging from 42 to 48 weeks (XALKORI®, Pfizer, Inc.). In many patients, loss of response manifests as systemic progression, but in many 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 clearer (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, L1152R, G1269A, S1206Y, F1174L, D1203N, C1156Y, T1151Tins, and G1202R mutations) may act by reducing the binding affinity of crizotinib to ALK (Bang, 2012). Other mechanisms of secondary resistance to crizotinib include the amplification of the ALK fusion gene, exploiting crizotinib's suboptimal potency against ALK, and the activation of alternate signaling pathways (Camidge et al, 2012; Katayama et al, 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 retains activity against all key crizotinib-resistance mutations and that can also achieve deep and prolonged target inhibition both systemically and in the CNS.

Additionally, due to some of the serious adverse effects that are associated with crizotinib treatment (pneumonitis, hepatic laboratory abnormalities, and QT prolongation), some patients experience unacceptable toxicities requiring dose reduction or dose interruption. When these toxicities are severe, discontinuation of crizotinib treatment is warranted. In the pivotal studies of crizotinib that supported its accelerated approval, 4% of (10/255) patients became "intolerant" to crizotinib and discontinued treatment due to an adverse event (AE).

7.2 AP26113 Nonclinical Summary

7.2.1 Nonclinical Activity against ALK

In nonclinical studies, AP26113 has been shown to:

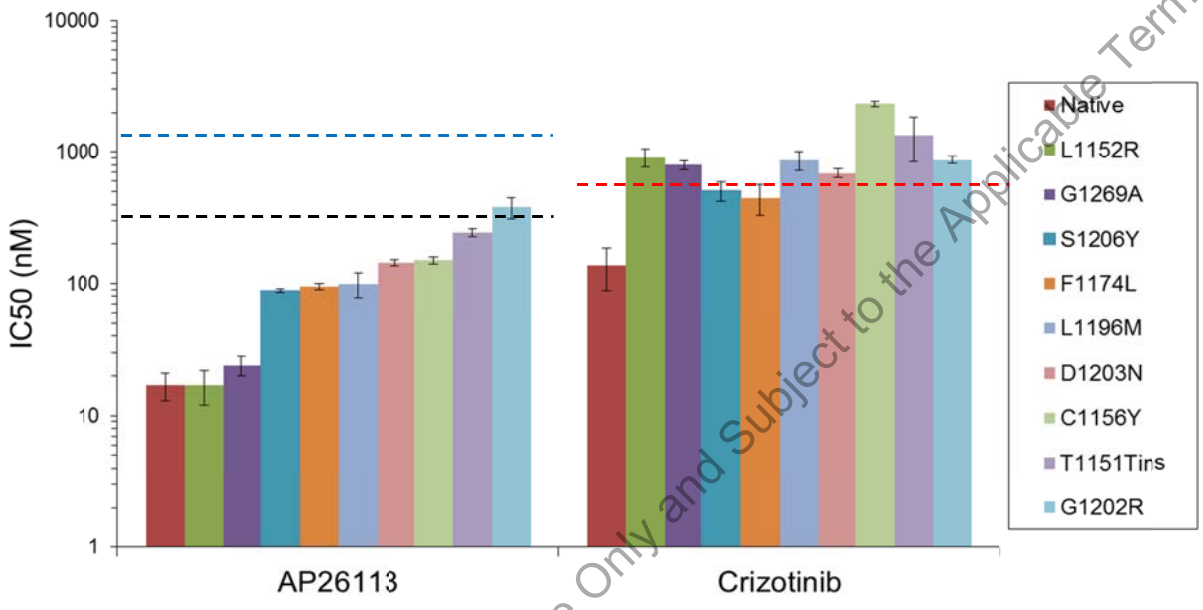
- Inhibit the activity of native ALK fusions with potency 8- to 10-fold greater than that of crizotinib
- Potently inhibit ALK variants that confer resistance to crizotinib in patients through acquisition of secondary mutations in ALK
- Suppress the emergence of any resistant ALK mutant in an in vitro assay, at concentrations that can be achieved clinically

Studies in cultured cell lines revealed that AP26113 potently and selectively inhibited growth of NSCLC cell lines positive for the oncogenic EML4-ALK genetic rearrangement (GI_{50}s of 4.2-10.1 nM) relative to EML4-ALK negative NSCLC lines (GI_{50}s of 503-1337 nM) (Rivera et al, 2010). AP26113 was approximately 10-fold more potent and 10-fold more selective than crizotinib at inhibiting growth of these cell lines.

To explore the activity of AP26113 against crizotinib-resistant ALK mutants, 9 different mutations that have been observed to date in the ALK kinase domain of crizotinib-resistant patient tumors were assessed in cellular viability assays. The viability of Ba/F3 cells dependent

on expression of the crizotinib-resistant ALK mutants was assessed in the presence of crizotinib or AP26113 (Figure 1).

Figure 1 AP26113 and Crizotinib Potency Relative to Clinically Achievable Plasma Levels



Source: American Society of Clinical Oncology. Abstract 8031; 2013.

50% maximal inhibitory concentration (IC_{50}) values of Ba/F3 cells dependent on expression of EML4-ALK (native) or kinase domain mutated EML4-ALK variants (n=9) treated with AP26113 or crizotinib. Data for each cell line is derived from at least 4 independent experiments (error bars = standard error). Dashed horizontal lines indicate the mean steady-state trough concentrations of each drug at the recommended phase 2 doses: AP26113 90 mg daily, 327 nM (black) and 180 mg daily, 1217 nM (blue); crizotinib 250 mg twice daily, 620 nM (red) (Kwak et al, 2010).

In this assay, AP26113 was 8-fold more potent than crizotinib at inhibiting viability of cells dependent on native EML4-ALK (50% maximum inhibitory concentrations [IC_{50}s] of 17 nM vs 137 nM). AP26113 was also more potent than crizotinib at inhibiting viability of mutant ALKdependent cells (13-fold average, 2- to 54-fold range). Further, whereas the crizotinib concentrations required to inhibit growth of mutant ALK-dependent cells typically exceeded the steady-state plasma concentrations observed in patients, AP26113 inhibitory concentrations were markedly lower than AP26113 steady-state plasma levels, particularly at a daily dose of 180 mg. These results suggest that ALK mutations confer crizotinib resistance in patients by sufficiently reducing crizotinib potency such that clinically achievable drug levels are ineffective at inhibiting ALK, and that AP26113 can be safely administered to patients at levels sufficient to inhibit crizotinib-resistant ALK mutants.

The studies described above demonstrated the ability of AP26113 to potently inhibit the activity of native EML4-ALK as well as 9 mutants previously observed to confer resistance to crizotinib. To determine whether there are other mutations in the kinase domain of EML4-ALK that can confer resistance to AP26113, an accelerated mutagenesis screen was performed (Zhang et al,

2010). This assay successfully identified mutations known to confer clinical resistance to crizotinib such as L1196M and F1174L. However, no mutations in ALK were identified that conferred resistance to 1 μM AP26113. Clinical pharmacokinetic data from the ongoing phase 1/2 study have shown that mean steady-state trough AP26113 plasma concentrations exceed 1 μM in NSCLC patients receiving180 mg daily (QD) (C_{trough} 1217 nM).

In summary, preclinical studies have revealed potent in vitro activity of AP26113 against oncogenic ALK, as well as mutant variants of oncogenic ALK that confer resistance to crizotinib in NSCLC patients. In addition, no ALK mutations have been identified in in vitro mutagenesis assays that can confer resistance to AP26113 at clinically achievable concentrations. Further details regarding nonclinical studies on in vivo antitumor activity, absorption, distribution, metabolism, and excretion (ADME) and toxicology performed with AP26113 can be found in the Clinical Investigator's Brochure for AP26113.

7.2.2 Nonclinical Activity against Other Targets

In vitro kinase assays have revealed that AP26113 has potent inhibitory activity against other kinases implicated in NSCLC including activated epidermal growth factor receptor (EGFR-L858R), ROS1, and CHK2, comparable to the inhibitory activity observed against ALK (IC_{50}s <10 nM). AP26113 also inhibits the in vitro kinase activity of the insulin-like growth factor 1 receptor (IGF-1R), which has high sequence homology to the ALK kinase domain, with an IC_{50} of 32 nM.

Additional in vitro and in vivo studies of AP26113 in relation to EGFR activity revealed that AP26113 does not inhibit native EGFR activity, but potently inhibits activated EGFR mutants commonly observed in NSCLC (eg, exon 19 deletion, L858R), as well as activated EGFR mutants containing the T790M gatekeeper mutation, which is known to confer resistance to other approved EGFR-TKIs such as erlotinib. These results have served as the basis for exploration in a phase 1/2 clinical study of AP26113 activity in EGFR mutant, T790M-positive NSCLC patients resistant to prior EGFR TKI treatment.

7.3 AP26113 Clinical Summary

Based on favorable preclinical in vitro and in vivo pharmacology and toxicology studies, a phase 1/2 clinical study of AP26113 (study AP26113-11-101) was initiated on 20 September 2011. Study 101 consists of a phase 1 dose escalation portion, followed by a phase 2 expansion portion with defined clinical cohorts. As of protocol amendment 1, the trial is still enrolling patients.

In the phase 1 dose-escalation portion of the study, patients were administered AP26113 at doses ranging from 30 mg QD to 300 mg QD. Twice-daily (BID) dose regimens were also evaluated in some patients during dose-escalation. At doses of 90 mg and higher, mean plasma steady-state trough drug concentrations that exceeded levels predicted preclinically to inhibit crizotinib-resistant ALK mutants were achieved. No dose-limiting toxicities (DLTs) were observed in the phase 1 portion of the trial at doses up to 180 mg QD. At higher doses, DLTs of grade 3 alanine aminotransferase (ALT) increased (240 mg QD) and grade 4 dyspnea (300 mg QD) were reported. The maximum tolerated dose (MTD) was not formally determined. However, based

on these results, the dose of 180 mg QD was initially chosen as the RP2D for the phase 2 expansion portion of the study.

In the phase 2 expansion portion of the study, 3 of 26 (12%) patients treated with 180 mg QD experienced early onset pulmonary symptoms that in some cases constituted pneumonitis (described in more detail below). Consequently, two additional RP2Ds were tested: 90 mg QD and a 7-day dosing period of 90 mg QD followed by escalation to 180 mg QD. Preliminary data (detailed below) support testing these regimens further in this randomized trial. The most up-to-date data can be found in the Clinical Investigator's Brochure for AP26113.

7.3.1 Overview of Safety Observations from the Phase 1/2 Trial

As of 6 September 2013, 91 patients were treated with AP26113 at doses ranging from 30 mg QD to 300 mg QD, including 45 patients treated at 180 mg QD. Of these, the median age was 57 years and 60% were female. The majority (82%) of patients were diagnosed with adenocarcinoma of the lung (NSCLC). Forty-two (46%) patients had a history of ALK rearrangement. Approximately half (51%) of patients had received one or two prior systemic treatment regimens while 24% received more than two prior systemic treatment regimens.

The most common treatment-emergent AEs (≥10% of patients) were nausea (38.5%), fatigue (34.1%), diarrhea (31.9%), cough (20.9%), headache (19.8%), dyspnea (16.5%), vomiting (16.5%), amylase increased (12.1%), decreased appetite (12.1%), and muscle spasms (11.0%). Treatment-related AEs of grade ≥3 occurring in 2 or more patients included dyspnea (4%), fatigue (3%), diarrhea (2%), hypoxia (2%), and pneumonitis (2%). Serious adverse events (SAEs) (treatment-related) occurring in 2 or more patients were dyspnea (7%), pneumonia (4%), hypoxia (2%), and pneumonitis (2%). Treatment-emergent AEs of grade 3 or higher are shown in Table 1.

Table 1 Treatment-emergent Adverse Events, Grade ≥3

Preferred term (≥2 patients)	30, 60 mg N=55 n (%)	90 mg N=8 n (%)	120 mg N=18 n (%)	180 mg* N=45 n (%)	240 mg N=12 n (%)	300 mg N=2 n (%)	Total N=91 n (%)
Dyspnea	0	0	1 (6)	1 (2)	1 (8)	1 (50)	4 (4)
Fatigue	1 (17)	0	0	1 (2)	2 (7)	0	4 (4)
Pneumonia	0	0	3 (17)	1 (2)	0	0	4 (4)
Hypoxia	0	0	0	1 (2)	1 (8)	1 (50)	3 (3)
Lung infection	0	0	1 (6)	1 (2)	0	0	2 (2)
Pneumonitis	0	0	1 (6)	1 (2)	0	0	2 (2)
Lipase increased	0	0	1 (6)	0	2 (17)	0	3 (3)
Diarrhea	0	0	0	0	2 (17)	0	2 (2)
Hyponatraemia	0	1 (13)	0	0	1 (8)	0	2 (2)

*Preferred terms ranked by incidence at 180 mg. Data extraction date: 6 September 2013.

Some patients experienced moderate or severe pulmonary AEs (dyspnea, pneumonia, hypoxia, lung infection, pneumonitis). One might expect a variety of pulmonary AEs in a lung cancer population. However, in the phase 2 expansion portion of study 101, the early onset of respiratory AEs was observed in 3 out of 26 patients dosed at 180 mg QD. In the study overall, there were 6 cases (13%) of an early onset syndrome in 45 patients dosed at 180 mg QD, and 4 additional cases observed at higher doses (2 at 240 mg QD and 2 at 300 mg QD) that comprise a

total of 10 cases (15%) in 59 patients treated with 180 mg QD or higher doses of AP26113 in the study. All 10 cases were SAEs.

These early pulmonary AEs were observed only at doses of 120 mg and higher, and were more frequent and more severe at higher doses. Most of these early pulmonary AEs occurred after a single dose of AP26113. Typically, patients with early grade 3 or 4 pulmonary AEs experienced shortness of breath on Day 1 or 2 after the first dose of AP26113. The temporal relationship to study drug administration suggests a causal relation to the drug. The reports of early onset dyspnea were associated in some cases with cough, chest tightness, or fever, and in more severe cases with oxygen desaturation and ground glass opacities on chest computed tomography (CT) scans, consistent with an acute pneumonitis and constituting SAEs. These events were reversible and responsive to AP26113 interruption and steroid support. In some patients, re-challenge resulted in recurrence of symptoms and discontinuation of treatment. One patient continued therapy after re-challenge, during which symptoms recurred but were amenable to medical management; some cases resolved with continued dosing in the absence of additional intervention. One patient with these symptoms died due to concurrent progressive metastatic disease, and the investigator assessed the death as possibly related to study drug administration.

Based on these safety observations, two additional potential RP2D regimens were tested in the phase 2 portion of the 101 study. The first is 90 mg QD for 7 days followed by dose escalation to 180 mg QD. That this regimen of initial lower dose exposure might ameliorate the early onset of pneumonitis is suggested by the observations that the pulmonary adverse event rate is dose-related, and not observed at 90 mg; and that symptoms typically occur within 48 hours of initial dosing but do not recur with continued exposure to AP26113, even at higher doses. As of 6 September 2013, 21 patients have been enrolled in the 101 study utilizing the 90 mg to 180 mg regimen. Twenty are evaluable for safety (1 patient was withdrawn after one dose when found to be ineligible for the study; the patient had no symptoms). One patient experienced a cough on Day 1, but continued dosing and escalated to 180 mg without further events. No other early onset pulmonary AEs or evidence of early pneumonitis were observed, and all patients' doses escalated to 180 mg. These data support the rationale of further testing of this regimen. The second potential RP2D regimen is 90 mg QD; at this dose, no early onset or grade 3 or 4 pulmonary AEs were observed in the phase 1 portion of the study and overall AE rates were low. At this time, additional patients are being enrolled to receive 90 mg QD.

7.3.2 Overview of Antitumor Activity

Antitumor activity has been observed in patients with crizotinib-resistant ALK+ NSCLC as well as in TKI-naïve patients. Overall, of the 34 ALK+ NSCLC patients treated with AP26113 who have been imaged, 22 responded (65% ORR; 95% CI: 47%-80%). In ALK+ NSCLC patients treated with prior crizotinib (and no other ALK TKIs), responses were documented in 19 out of 28 patients (68% ORR; 95% CI: 48%-84%). An ORR of 100% was observed for TKI-naïve patients (3/3), including one complete response. Response duration ranged from 8+ to 40+ weeks in 14 patients with confirmed responses. In addition, 8 of 10 ALK+ NSCLC patients with active CNS lesions at baseline had evidence of radiographic improvement in the CNS (duration of CNS benefit in these patients ranged from 8+ to 40+ weeks). Responses in CNS lesions were observed in patients receiving 180 mg QD or higher. Overall response rates and CNS response rates by dose cohort are shown in Table 2.

Table 2 Overall Response Rates and CNS Response Rates by Dose Cohort

Dose[#]	ORR Evaluable* (N)	ORR** (N, %)	CNS Evaluable*** (N)	CNS RR (N, %)
30 mg	0	NA	0	NA
60 mg	1	1 (100)	0	0
90 mg	6	6 (100)	0	0
120 mg	5	4 (80)	0	0
180 mg	21	11 (52)	7	6 (86)
240 mg	5	3 (60)	3	2 (67)
300 mg	0	NA	0	NA
90-180 mg	NA	NA	NA	NA

[#]Some patients received BID dosing; *ORR evaluable are patients with ALK+ NSCLC who had discontinued or undergone at least one scan at the time of reporting; **ORR: overall response rate; ***CNS evaluable are patients with active CNS disease (symptomatic or progressive) who had discontinued or undergone at least one scan at the time of reporting. Data extraction date: 6 September 2013.

7.3.3 Pharmacokinetics

Pharmacokinetic (PK) data from study 101 suggest that plasma AP26113 exposures (maximum plasma concentration [C_{max}], steady-state trough plasma concentration [C_{trough}]) generally increase with increasing dose. At doses of 90 mg QD and higher, the mean AP26113 plasma concentration at steady-state (Day 29 C_{trough}) exceeded the preclinically-defined IC_{50} values required to inhibit native ALK and 9 mutant ALK variants that confer resistance to crizotinib. The half-life of AP26113 is approximately 25-28 hours.

7.3.4 Rationale for Proposed RP2Ds

Based on observations made from the phase 1/2 study, two RP2Ds are recommended for further study. As might be expected, a higher incidence of AEs occurs with higher doses of AP26113, and grade 3 or 4 AEs are more frequent as well. However, there is no clearly defined relationship between dose and antitumor activity at doses above 60 mg, although the dose escalation cohorts enrolled small numbers of patients that prevent drawing firm conclusions regarding response rates. At 90 mg, mean plasma drug concentrations that surpass those that result in vitro in resistant mutant ALK inhibition are achievable. Thus, there is a rationale for further testing in phase 2 studies of 90 mg QD, the minimum dose where adequate plasma drug concentration and antitumor activity (6/6 responses in evaluable patients) are coupled with a desirable safety profile.

However, although preclinically defined active drug concentrations can potentially help interpret drug concentrations in the blood in the context of antitumor activity, or even assist in establishing minimum target concentrations, they are not precisely predictive of efficacious clinical doses. Higher drug concentrations might be necessary to overcome all mutational, as well as non-mutational, factors that contribute to resistance such as those that interfere with drug access to target at both the cellular and organ level. Of particular import for ALK+ NSCLC patients whose treatment has failed is that brain metastases are a well identified sanctuary site from antitumor agents, and especially from crizotinib (Camidge et al, 2012; Costa et al, 2011).

Numerous authors have hypothesized that higher drug concentrations enable penetration of the CNS by active agents to potential therapeutic advantage (Bachelot et al, 2013; Togashi et al, 2012). In the 101 phase 1/2 study, CNS response rates utilizing at least 180 mg QD are high. Moreover, higher concentrations may contribute to rapidity of response to drug, depth of response, and durability of response, all characteristics that cannot be studied well in a phase 1 setting. Thus, there is a rationale to further test higher doses as well. Initially, 180 mg QD was selected as a RP2D, but the observed incidence of early pulmonary AEs precludes utilizing this dose. The addition of a 90-mg QD 7-day lead-in to therapy with 180 mg QD appears to lessen the incidence of early pneumonitis and pulmonary symptoms. Therefore, this dose will be tested as a RP2D as well. In summary, AP26113 was generally safe at doses up to 180 mg QD in the phase 1/2 trial. AP26113 exhibited substantial anticancer activity in patients with crizotinib-resistant ALK+ NSCLC. AP26113 is also active in ALK+ brain metastases with frequent responses of clinically meaningful duration. Two RP2Ds have been determined for further study.

7.4 Rationale for the Phase 2 AP26113 Clinical Study

There continues to be a need to explore new treatment options for patients who have experienced failure of crizotinib due to resistance or intolerance. Chemotherapy is an approved treatment option for such patients although it is not specifically approved for use in ALK+ NSCLC patients. In an unselected NSCLC population, first-line (doublet) chemotherapy typically yields ORRs of 30% (median PFS: 4 to 5 months) and second-line (single-agent) chemotherapy yields ORRs <11% (PFS: 2.9 months) (Shepherd et al, 2000; Fossella et al, 2000; Hanna et al, 2004; Shepherd et al, 2005; Kim et al, 2008; Shaw et al, 2012; Solomon et al, 2013). New therapies are needed to improve response rates, to provide greater durability of response, and to overcome resistance to crizotinib. Like all cancers, ALK+ NSCLC is a serious condition, and patients who have experienced failure of crizotinib likely have increased morbidity and mortality.

Based on the promising activity profile of AP26113 in vitro and in vivo and the clinical activity demonstrated in the phase 1/2 study, this phase 2 study will evaluate AP26113 using two dosing regimens. Patients with ALK+ NSCLC who have experienced failure of crizotinib therapy will be randomized 1:1 to receive either 90 mg QD continuously (in Arm A) or a lead-in dose of 90 mg QD for 7 days followed by 180 mg QD continuously (in Arm B).

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study is to determine the efficacy of AP26113, as evidenced by objective response rate, in patients with ALK-positive locally advanced or metastatic NSCLC whose disease has progressed on therapy with crizotinib. Two dosing regimens will be tested.

8.2 Secondary Objectives

The secondary objectives of the study (for each dosing regimen) are:

1. To further characterize the efficacy of AP26113 in patients with ALK-positive, locally advanced or metastatic NSCLC whose disease has progressed on therapy with crizotinib,

as shown by disease control rate, time to/duration of response, progression-free survival (PFS), overall survival (OS), and time on treatment

2. To assess CNS response and PFS, per RECIST v1.1, in those patients who have active brain metastases
3. To assess the safety and tolerability of AP26113 in study patients
4. To measure steady-state plasma levels of AP26113 for use in 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)

8.3 Exploratory Objectives

CCI

[redacted]

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a phase 2, open-label, randomized, multicenter, international study. The patient population will include patients with ALK-positive, locally advanced or metastatic NSCLC whose disease has progressed on therapy with crizotinib. An estimated 218 patients will be enrolled at approximately 100 centers. The primary objective of the study is to determine the efficacy of two dosing regimens of AP26113 by confirmed ORR, as assessed by the investigator, in this patient population. Secondary objectives include additional efficacy assessments and assessments of safety, tolerability, PK, and quality of life. Patients will be randomized 1:1 to receive AP26113 in one of two different dosing regimens. In Arm A, AP26113 will be administered at a dose of 90 mg QD, continuously. In Arm B, AP26113 will be administered at a dose of 90 mg QD for 7 days, then 180 mg QD, continuously. A cycle of therapy will comprise 28 days of treatment, regardless of dose.

Throughout the study, AEs will be assessed and categorized by the US National Cancer Institute (US) 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 remain on treatment until they meet one or more criteria for withdrawal as listed in Section 11.9. Patients will be supplied study drug until they discontinue from the study.

9.1.1 Primary Endpoint

Confirmed Objective Response Rate (ORR), as assessed by the investigator, per RECIST v1.1.

9.1.2 Secondary Endpoints

1. Confirmed ORR, as assessed by a central independent review committee (IRC), per RECIST v1.1

2. CNS response (ORR and PFS, per RECIST v1.1, in patients who have active brain metastases)
3. Time to response
4. Duration of response
5. Time on treatment
6. Disease control rate (the percentage of patients with best response of complete response [CR], PR, or SD), per RECIST v1.1
7. Progression-free survival (PFS)
8. Overall survival (OS)
9. Safety and tolerability
10. Steady-state plasma level of AP26113 for use in population PK modeling
11. Patient-reported symptoms of lung cancer and HRQoL scores, assessed with the EORTC QLQ-C30 (v3.0)

9.1.3 Exploratory Endpoints

CCI

[redacted]

9.2 Randomization

Patients will be randomized in a 1:1 ratio to receive either 90 mg QD continuously or 90 mg QD for 7 days followed by 180 mg QD continuously. Patients will be stratified by the following two factors, each having two levels:

1. Brain metastases at baseline (present vs absent)
2. Best prior response to crizotinib therapy as assessed by the investigator (CR or PR vs any other response or status unknown)

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

10 SELECTION OF STUDY POPULATION

10.1 Inclusion Criteria

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.

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

1. Have histologically or cytologically confirmed locally advanced or metastatic NSCLC that is ALK+.
2. Must meet one of the following two criteria:
   a. Have documented ALK rearrangement by a positive result from the Vysis® ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit; or
   b. Have documented ALK positivity by a different test and tissue available for the Vysis® FISH test. Tissue should be derived preferably from a biopsy taken after progression with crizotinib. If such a sample is not available, testing may be performed with archived tumor tissue.
3. Had progressive disease while on crizotinib, as assessed by the investigator or treating physician.
4. No longer a required criterion as of Amendment 2.
5. Have at least 1 measurable lesion per RECIST v1.1 (see Appendix C). Note: Previously irradiated lesions may not be used for target lesions, unless there is unambiguous radiological progression after radiotherapy. Brain lesions may not be used as target lesions if they were: 1) previously treated with whole brain radiation therapy (WBRT) within 3 months, or 2) previously treated by stereotactic radiosurgery (SRS) or surgical resection.
6. No longer a required criterion as of Amendment 2.
7. Recovered from toxicities related to prior anticancer therapy to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, v4.0) grade ≤2 (see Appendix A).
8. Are a male or female patient ≥18 years old.
9. Have a life expectancy ≥3 months.
10. Have adequate organ and hematologic function, as determined by:
    a. Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤2.5 x upper limit of normal (ULN; ≤5 x ULN is acceptable if liver metastases are present)
    b. Total serum bilirubin ≤1.5 x ULN (<3.0 x ULN for patients with Gilbert syndrome)
    c. Serum creatinine ≤1.5 x ULN
    d. Serum lipase/amylase ≤1.5 x ULN
    e. Absolute neutrophil count (ANC) ≥1500/µL
    f. Platelets ≥75000/µL
    g. Hemoglobin ≥10 g/dL
11. Have Eastern Cooperative Oncology Group (ECOG) performance status ≤2 (see Appendix B).
12. Have normal QT interval on screening electrocardiogram (ECG) evaluation, defined as QT interval corrected (Fridericia) (QTcF) of ≤450 ms in males or ≤470 ms in females.

13. For female patients of childbearing potential, a negative pregnancy test must be documented prior to enrollment.
14. Female and male patients who are fertile must agree to use a highly effective form of contraception with their sexual partners throughout study participation (Section 14.3.1).
15. Must provide a 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.
16. Have the willingness and ability to comply with scheduled visits and study procedures.

10.2 Exclusion Criteria

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

1. Received any prior ALK-targeted TKI other than crizotinib.
2. Received crizotinib within 3 days of the first dose of AP26113 (Day 1, Cycle 1).
3. Received cytotoxic chemotherapy, investigational agents, or radiation within 14 days, except SRS or stereotactic body radiosurgery.
4. Received monoclonal antibodies or had major surgery within 30 days of the first dose of AP26113 (Day 1, Cycle 1).
5. Have been diagnosed with another primary malignancy within the past 3 years (except for adequately treated non-melanoma skin cancer, cervical cancer in situ, or prostate cancer, which are allowed within 3 years).
6. Have symptomatic CNS metastases that are neurologically unstable or require an increasing dose of corticosteroids.
7. Have current spinal cord compression.
8. 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 AP26113
    b. Unstable angina within 6 months prior to first dose
    c. Congestive heart failure (CHF) within 6 months prior to first dose
    d. History of clinically significant (as determined by the treating physician) atrial arrhythmia
    e. Any history of ventricular arrhythmia
    f. Cerebrovascular accident or transient ischemic attack within 6 months prior to first dose
9. Have a history or the presence of pulmonary interstitial disease or drug-related pneumonitis.
10. Have an ongoing or active infection. The requirement for intravenous (IV) antibiotics is considered active infection.
11. Have a known history of human immunodeficiency virus (HIV). Testing is not required in the absence of history.

12. Have a history of or active significant gastrointestinal (GI) bleeding within 3 months of the first dose of AP26113.
13. Have a known or suspected hypersensitivity to AP26113 or its excipients.
14. Have malabsorption syndrome or other GI illness that could affect oral absorption of the study drug.
15. Have any condition or illness that, in the opinion of the investigator, would compromise patient safety or interfere with evaluation of the drug study.
16. Be pregnant or breastfeeding.

11 STUDY PROCEDURES

Informed consent, documented by a signed consent form, must be obtained prior to any screening activities not otherwise part of the patient's care. The *screening period* begins when the informed consent form is signed, and continues until the first dose of study drug is administered. The *follow-up period* begins after the last completed site visit and continues until patient contact discontinues.

11.1 Study Procedure Descriptions

The study procedures to be performed at screening and throughout 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.

The following list describes the procedures/tests required for this study.

1. Screening

Patients with known locally advanced or metastatic NSCLC, ALK+ status, and history of prior crizotinib 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 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, hematology, chemistry, insulin, testosterone (male patients), urinalysis and PT/PTT, and pregnancy test assessments do not need to be repeated on Day 1 if they were performed for screening within 7 days prior to 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 (refer to item 21 for further details).

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 part of the patient's care.

3. Randomization

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

4. Demographics

Demographic information 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, 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 staging at the time of screening, along with tumor histology, and sites of primary and metastatic disease, should be recorded.

7. Prior Cancer Therapy

Prior cancer therapy history consists of cancer-related surgical procedures, radiation, and systemic therapies. Surgical procedures include curative and diagnostic procedures (for example, biopsy). Radiation will include both definitive and palliative treatment, and systemic therapy should include all regimens given and each drug name in a regimen, the start and stop dates of each drug and 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. (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 must submit tissue samples for analysis using the Vysis® ALK Break-Apart FISH Probe Kit. Specifications regarding handling and processing of tissue for this test are described under item 23 below (Tumor Tissue Samples) and in the Study Reference Manual.

9. Physical Examination

A complete physical examination must be performed at screening and/or on Cycle 1, Day 1 prior to the first dose of AP26113, 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 the adverse reactions reported during treatment with crizotinib, investigators are cautioned to monitor patients treated with AP26113 for signs of vision dysfunction as well. The End-of-Treatment physical examination should be a complete physical examination. The 30 day after treatment physical examination 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.

11. ECOG Performance Status

The patient's performance status must be assessed using the ECOG performance scale during screening and/or on Cycle 1, Day 1 prior to the first dose of AP26113. The ECOG performance scale is provided in Appendix B.

12. Hematology

Hematology measurements include complete blood count (CBC) with differential and platelet count. Cycle 1, Day 1 hematology blood draws should be performed prior to the first dose of AP26113.

13. Chemistry

Serum chemistry consists of a peripheral blood draw with the following assessments: 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 and lipase, and glucose. The serum chemistry blood draws at screening and on Cycle 2, Day 1 (and all blood draws for glucose) should be performed in a fasting state, which should be noted. Cycle 1, Day 1 serum chemistry blood draws should be performed prior to the first dose of AP26113.

14. Urinalysis

Urinalysis will include pH, specific gravity, protein, ketones, glucose, urobilinogen, and occult blood. Cycle 1, Day 1 urinalysis blood draws should be performed prior to the first dose of AP26113.

15. Insulin

Serum insulin and glucose should be measured concurrently. All insulin and glucose blood draws should be performed in a fasting state, which should be noted. Cycle 1, Day 1 insulin blood draws should be performed prior to the first dose of AP26113.

16. Testosterone Level (males only)

In male patients, serum testosterone should be measured at screening or Cycle 1, Day 1 (prior to the first dose of AP26113); and per the Schedule of Events throughout the study.

17. Prothrombin Time/Partial Thromboplastin Time

Prothrombin time (PT) will be expressed as an International Normalized Ratio (INR) or in seconds (the latter against control). Partial thromboplastin time (PTT) will be expressed in seconds.

18. Electrocardiogram

All electrocardiograms (ECGs) must be 12-lead ECGs.

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/3√RR interval) method must be used for all calculations of heart rate-corrected QT (calculated) (QTc) intervals.

19. Adverse Events

AEs are to be recorded continuously throughout the entire study and graded per NCI CTCAE version 4.0 (See Appendix A).

20. Concomitant Treatments

Concomitant treatments for all ongoing medical history conditions or AEs 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.

21. 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. Women of childbearing potential at study start must also complete the pregnancy test once every 3 cycles thereafter and at the End-of-Treatment.

22. Disease Assessment CT/MRI, Brain MRI

At screening, disease assessment must include imaging of the chest and abdomen (covering adrenal glands), using appropriate radiological procedures (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 and will be repeated post-baseline for patients with CNS metastases. All radiographic images (eg, CT scan, MRI) performed during the study will be submitted to the imaging core laboratory for central review.

Disease assessment by CT or MRI scans will be performed at screening and at 8-week intervals thereafter (on Day 1 [±3 days] of every odd-numbered cycle) through 15 cycles after the initial dose of AP26113, and every 3 cycles thereafter until disease progression.

More-frequent imaging is recommended at any time, if clinically indicated; confirmation of CR or PR can be performed at least 4 weeks after initial response. Imaging assessment will also be performed at the End-of-Treatment if more than 4 weeks have passed since the last imaging assessment.

For patients who continue the study treatment beyond documented progressive disease per RECIST v1.1 at the investigator's discretion, imaging will continue with the same assessment schedule. If the patient experiences symptomatic deterioration in the absence of radiologic progression, it is strongly recommended that additional imaging studies be performed to confirm progressive disease.

23. Tumor Tissue Samples

Screening:

*Patients who have **not** had a prior Vysis® ALK Break-Apart FISH Probe Kit test performed:*

Formalin-fixed, paraffin-embedded (FFPE) tumor tissue must be provided for testing with the Vysis® ALK Break-Apart FISH Probe Kit. Details of sample provision are provided in the Study Reference Manual.

All patients:

If available, FFPE tumor tissue that was acquired **after** progression on crizotinib must be provided for exploratory molecular genetic analysis. If sufficient tissue cannot be made available (see the Study Reference Manual for minimum requirements), the sponsor must be informed prior to patient enrollment.

End-of-Treatment:

An optional end-of-treatment biopsy will be taken at time of AP26113 progression for patients who consent to the procedure and test. CCI [redacted]

24. CCI [redacted]

CCI

[redacted]

25. Plasma Samples for Steady-State AP26113 Concentration

All patients must provide a blood sample (approximately 3 mL per sample) for analysis of steady-state AP26113 plasma concentration. Samples will be collected on Day 1 of Cycles 2, 3, 4, and 5. Cycle 2 requires sampling at pre-dose, and at 1 hour (±10 minutes), 4 hours (±15 minutes) and 6-8 hours (±15 minutes) post-dose. During Cycles 3, 4, and 5, samples will be collected at two time points from each patient (a pre-dose sample and a second sample anytime between 1 to 8 hours post-dose). Patients must be instructed not to take the day's dose of AP26113 until after the pre-dose plasma sample is collected. The pre-dose sample should be collected as close as possible to 24 hours after the prior dose; administration time of prior dose must be recorded, along with time of the pre-dose PK sample.

26. Patient-Reported Outcomes Questionnaire

The patient-reported outcomes (PRO) questionnaire (EORTC QLQ-C30) will be administered at specified scheduled visits and at the visit 30 days after the last dose of AP26113. The PRO questionnaire should be administered to patients when they arrive for their scheduled visits, **prior to** any clinical measurements, assessments, evaluations, or procedures being performed.

27. End-of-Treatment

End-of-Treatment assessments must be performed when the decision is made to permanently discontinue AP26113, but within 21 days after the last dose of AP26113. Physical examinations, laboratory tests (hematology, chemistry, urinalysis, insulin, PT, PTT), and ECG can 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.

28. 30 Days After Last Dose

The 30 Days After Last Dose assessments must be performed 30 days (±3 days) after the last dose of AP26113. Physical examinations and laboratory tests (hematology, chemistry, urinalysis, insulin, PT, PTT), 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 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-Day Post-Last Dose assessments, information may be collected from tests performed for the study or as part of the patient's routine medical care.

29. Follow-up

Patients will be followed throughout the study, as per Table 3. The follow-up assessments (ie, contacting the patient for survival and subsequent anticancer therapy) must be performed every 3 months after the End-of-Treatment. The allowable window for follow-up assessments is 14 days. Follow-up will continue for 2 years after the last patient enrolls into the study.

Table 3 Schedule of Events

	Screening Period	Treatment through 30 Days After Last Dose								Follow-up Period
Assessment	**Screening[1]**	**Cycle 1 (28 Days)**			**Every 4 weeks (Day 1 of each cycle from Cycle 2 onwards)**	**Every 8 weeks (from Day 1 of Cycle 3 through Cycle 15; every 3 cycles thereafter)**	**Every 12 weeks (Day 1 of every 3rd cycle from Cycle 4 onwards)**	**End-of-Treatment[27]**	**30 Days After Last Dose[28]**	**Follow-up[29]**
Day (D)	**D-14 to D0**	**D1**	**D8**	**D15**						
Informed Consent[2]	X									
Randomization[3]	X									
Demographics[4]	X									
Medical/Surgical History[5]	X									
Diagnosis and Cancer History[6]	X									
Prior Cancer Therapy[7]	X									
ALK Mutation Status[8]	X									
Physical Examination[9]	X	X	X*	X*	X			X	X	
Vital Signs[10]	X	X	X	X	X			X	X	
ECOG Performance Status[11]	X	X			X			X	X	
Hematology[12]	X	X		X	X			X	X	
Chemistry (fasting, if possible)[13]	X	X		X	X			X	X	
Urinalysis[14]	X	X			X			X	X	
Insulin (fasting, if possible)[15]	X	X		X	X			X	X	
Testosterone Level (males only)[16]	X	X			X			X	X	
Prothrombin Time (PT)/Partial Thromboplastin Time (PTT)[17]	X	X		X	X			X	X	

	Screening Period	Treatment through 30 Days After Last Dose								Follow-up Period
Assessment	**Screening[1]**	**Cycle 1 (28 Days)**			**Every 4 weeks (Day 1 of each cycle from Cycle 2 onwards)**	**Every 8 weeks (from Day 1 of Cycle 3 through Cycle 15; every 3 cycles thereafter)**	**Every 12 weeks (Day 1 of every 3rd cycle from Cycle 4 onwards)**	**End-of-Treatment[27]**	**30 Days After Last Dose[28]**	**Follow-up[29]**
Day (D)	**D-14 to D0**	**D1**	**D8**	**D15**						
Electrocardiogram (ECG)[18]	X	X			X			X	X	
Adverse Events[19]	Throughout Study									
Concomitant Treatments[20]	Throughout Study									
Pregnancy Test[21]	X	X					X	X		
Disease Assessment CT/MRI scans[22]	X					X		X		
Brain MRI[22]	X					X				
Tissue for ALK FISH Testing[23]	X									
Post-Crizotinib Tissue for Molecular Genetics[23]	X									
End-of-Treatment Tissue Sample for Molecular Genetics[23]								X		
CCI [redacted]										
Plasma Sample for Steady-state AP26113 Concentration[25]					X					
Patient-Reported Outcomes Assessment[26]	X	X			X			X	X	
Subsequent Anticancer Therapy/Survival[27]										X

*Assessment for early pulmonary symptoms must be performed during the visit on Day 8 and Day 15. For numbered table footnotes, see Section 11.1.

11.2 Screening Period

The screening period begins when the informed consent form is signed, and continues until the first dose of AP26113 is administered. 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. 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

This period begins when the patient receives the first dose of AP26113.

Assessments required during this period are shown in Table 3. 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 treatment (which may be after a dose interruption).

Assessments required at End-of-Treatment are shown in Table 3. A detailed description of procedures and timing is provided in Section 11.1.

11.6 30 Days After Last Dose

Assessments required at 30 Days After Last Dose are shown in Table 3. A detailed description of procedures and timing is provided in Section 11.1.

11.7 Follow-up Period Procedures

The follow-up period for a patient begins after the last completed site visit and continues until patient contact ceases (for at least 2 years after the last patient has enrolled).

Assessments required for the Follow-up Period are shown in Table 3. 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 AP26113 until they experience disease progression or intolerable toxicity. Treatment may be continued after progression, at the discretion of the investigator. On Arm A, at the time of progression, the patient may continue at the same dose or the patient's dose may be escalated from 90 mg QD to 180 mg QD. For patients on either arm

receiving 180 mg QD, at the time of progression, treatment may continue if there is still evidence of clinical benefit (see Section 13.1.2 for details on treatment continuation after progression).

11.8.2 Approximate Duration of Study

The total estimated duration of the study is at least 3 years, including approximately 18 months to accrue patients, with 2 years for treatment and follow-up for the last patient. Patients will be allowed to receive study drug beyond this period until disease progression or they discontinue treatment for other reasons.

11.9 Patient Discontinuation

Patients will be discontinued from further study drug 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: In some cases, despite progression by RECIST v1.1, patients and investigators may have the opinion that continued study drug administration is beneficial and, in these cases, therapy may continue).
- 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 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 will 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 who receives study drug. An End-of-Treatment reason must be recorded for any patient who receives study drug.

If a patient is discontinued from the study 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). 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 discontinue prematurely from study treatment will be followed-up for survival every 3 months after the last dose of AP26113.

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, investigator, and medical monitor. 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 treatment;
- 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 will be determined per RECIST v1.1 (see Appendix C) by the investigator, with a secondary independent radiological review. Evaluation of efficacy will be by ORR (confirmed ≥4 weeks after initial response), disease control rate (CR, PR, SD), time to/duration of response, PFS, OS, and time on treatment. CNS response will be evaluated by ORR and PFS.

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

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) questionnaire, which has been studied extensively, is validated, and is suitable for use in global clinical studies. The questionnaire will be administered to patients in their local language.

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).

Note: Signs and symptoms assessed with the EORTC QLQ-C30 (v3.0) will not be considered AEs.

13 STUDY TREATMENT(S)

13.1 Study Drug

AP26113 is an investigational drug that will be administered only to eligible enrolled patients at qualified centers (for example, listed on the FDA Form 1572).

13.1.1 Treatment Administration

Patients will be randomized 1:1 to receive AP26113 in one of two different dosing regimens. In Arm A, AP26113 will be administered at a dose of 90 mg orally QD, continuously. In Arm B, AP26113 will be administered at a dose of 90 mg orally QD for 7 days, then 180 mg QD orally, continuously. A cycle of therapy will comprise 28 days of treatment, regardless of dose.

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. Missed doses should be recorded in an appropriate source record (eg, clinic chart), patient diary card, and study drug administration eCRF.

Study drug administration will continue until the patient dies, discontinues treatment, or the trial ends. In some cases, despite progression by RECIST v1.1, patients and investigators may have the opinion that continued study drug administration is beneficial and, in these cases, therapy may continue.

13.1.2 Continued Treatment after Disease Progression

Patients will continue to be dosed with AP26113 until they experience disease progression or intolerable toxicity. In certain circumstances, at the discretion of the treating investigator, therapy may continue after progressive disease has been identified.

Candidates for Dose Escalation on Arm A

Patients on Arm A being treated at 90 mg QD who experience progressive disease will be allowed, at the discretion of the treating investigator, to escalate their dose to 180 mg QD. According to the investigator's assessment, the risk posed to the patient by dose escalation must be acceptable, and must be outweighed by the potential benefit of continued treatment. Patients who have undergone dose reduction for adverse events to 60 mg are not candidates for escalation to 180 mg QD.

Continued Therapy at the Time of Disease Progression on Either Arm

Patients in either arm who experience disease progression may continue to be treated at the same dose if in the opinion of the treating investigator they continue to experience benefit.

13.1.3 Dose Modification(s)

13.1.3.1 Dose Modifications for Treatment-related Adverse Events

The following sections provide recommended dose modification guidelines for treatment-related adverse events observed with AP26113 administration. Dose modification guidelines specific to the management of early onset pulmonary syndrome and pneumonitis are provided in Sections 13.1.4.1 and 13.1.4.2.

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 a treatment-related AE does not resolve to grade 1 or less after dose interruption for more than 28 days, the patient must be discontinued from study treatment. Additionally, the sponsor's Medical Monitor must be contacted if any AE deemed unrelated to treatment requires dose interruption for more than 28 days.

13.1.3.1.1 Dose Modifications for Arm A (90 mg QD)

Criteria for dose modifications of general treatment-related adverse events (excluding early onset pulmonary syndrome and pneumonitis) in patients initially treated with 90 mg QD are recommended in Table 4.

Table 4 Arm A AP26113 Dose Modification Recommendations for Treatment-related Adverse Events (Excluding Pneumonitis)

Toxicity Grade per CTCAE v4.0	Recommended Action
Nonhematologic Toxicity	
Grade 1	Manage the toxicity with supportive care while continuing at the same dose
Grade 2	Manage the toxicity with supportive care while continuing at the same dose
Grade 3	When the current dose is 90 mg QD: Hold until event is ≤Grade 1, or has returned to baseline Resume at 90 mg or 60 mg QD at the discretion of the investigator Upon recurrence at 90 mg QD: Hold until event is ≤Grade 1, or has returned to baseline Resume at 60 mg QD When the current dose is 60 mg QD: Consider discontinuing treatment
Grade 4	When the current dose is 90 mg QD: Hold until event is ≤Grade 1, or has returned to baseline Resume at 60 mg QD, or discontinue, at the discretion of the investigator When the current dose is 60 mg QD: Consider discontinuing treatment
QTc Prolongation	
Grade 1 (QTcF 450-480 ms)	Review concomitant medications and perform serum electrolyte analysis (including potassium, calcium, and magnesium). Manage the toxicity with supportive care and correct with supplements if electrolytes are below normal limits. Continue at the same dose.
Grade 2 (QTcF 481-500 ms)	First occurrence at any dose level: Hold treatment Perform serum electrolyte analysis (including potassium, calcium, and magnesium) and correct with supplements if below normal limits Review concomitant medications Repeat ECG as clinically indicated, but at least daily until QTcF returns to ≤ Grade 1 (480 ms) Resume at current dose after recovery to ≤ Grade 1 If no contributing reason was identified for QTcF elevation, then weekly ECG monitoring is recommended for 4 weeks upon resumption of treatment, then monthly for 6 months, and then every 3 months for the remainder of the study, or more frequently as clinically indicated Upon recurrence at 90 mg QD: Repeat above Hold until event is ≤ Grade 1, or has returned to baseline Resume at 60 mg QD Upon recurrence at 60 mg QD: Consider discontinuing treatment
Grade 3 (QTcF ≥ 501 ms on at least 2 separate ECGs)	First occurrence at any dose level: Hold treatment Perform serum electrolyte analysis (including potassium, calcium, and

	magnesium) and correct with supplements if below normal limits Review concomitant medications Repeat ECG as clinically indicated, but at least daily until QTcF returns to ≤ Grade 1 (480 ms) Resume at next lower dose level after recovery to ≤ Grade 1 If no contributing reason was identified for QTcF elevation, then weekly ECG monitoring is recommended for 4 weeks upon resumption of treatment, then monthly for 6 months, and then every 3 months for the remainder of the study, or more frequently as clinically indicated Upon recurrence at 90 mg QD: Repeat above Hold until event is ≤ Grade 1, or has returned to baseline Resume at 60 mg QD Upon recurrence at 60 mg QD: Consider discontinuing treatment
Grade 4 (QTc ≥501 or >60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Consider discontinuing treatment
Hematologic Toxicity	
Grade 1	Continue at current dose
Grade 2	Continue at current dose
Grade 3	When the current dose is 90 mg QD: Hold until event is ≤Grade 2, or has returned to baseline Resume at 90 mg or 60 mg QD at the discretion of the investigator Upon recurrence at 90 mg QD: Hold until event is ≤Grade 2, or has returned to baseline Resume at 60 mg QD When the current dose is 60 mg QD: Consider discontinuing treatment
Grade 4	When the current dose is 90 mg QD: Hold until event is ≤Grade 2, or has returned to baseline Resume at 60 mg QD When the current dose is 60 mg QD: Consider discontinuing treatment

13.1.3.1.2 Dose Modifications for Arm B (90 mg QD Day 1-7 Followed by 180 mg QD)

Dose Modifications for Patients Prior to Dose Escalation

Criteria for dose modifications for treatment-related AEs prior to dose escalation, in the first 7 days of treatment (excluding early onset pulmonary syndrome and pneumonitis) are recommended in Table 5.

Table 5 Arm B AP26113 Dose Modification Recommendations for Treatment-related Adverse Events (Excluding Pneumonitis) prior to Dose Escalation

Toxicity Grade per CTCAE v4.0	Action for Dose Modification	Criteria for Dose Escalation
Nonhematologic Toxicity		
Grade 1	Manage the toxicity with supportive care while continuing at the same dose.	Escalate to 180 mg QD on Day 8, as scheduled.
Grade 2 (≤3 days)	Manage the toxicity with supportive care while continuing at the same dose.	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.
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.

13.1.3.1.3 Dose Modifications after Dose Escalation to 180 mg QD for Patients in Arm B

For patients in Arm B, after the initial treatment period at 90 mg QD, the dose should be escalated to 180 mg QD after 7 days, or the dose modification guidelines above should be followed.

Criteria for dose modifications for treatment-related AEs after dose escalation for patients in Arm B (excluding early onset pulmonary syndrome and pneumonitis) are recommended in Table 6.

Table 6 Arm B AP26113 Dose Modification Recommendations for Treatment-related Adverse Events (Excluding Pneumonitis) after Dose Escalation Period*

Toxicity Grade per CTCAE v4.0	Recommended Action
Nonhematologic Toxicity	
Grade 1	Manage the toxicity with supportive care while continuing at the same dose
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
QTc Prolongation	
Grade 1 (QTcF 450-480 ms)	Manage the toxicity with supportive care such as reviewing concomitant medications and performing serum electrolyte analysis (including potassium, calcium, and magnesium) and correct with supplements if below normal while continuing at the same dose
Grade 2 (QTcF 481-500 ms)	First occurrence at any dose level: Hold treatment Perform serum electrolyte analysis (including potassium, calcium, and magnesium) and correct with supplements if below normal limits Review concomitant medications Repeat ECG as clinically indicated, but at least daily until QTcF returns to ≤

	Grade 1 (480 ms) Resume at current dose after recovery to ≤ Grade 1 If no contributing reason was identified for QTcF elevation, then weekly ECG monitoring is recommended for 4 weeks upon resumption of treatment, then monthly for 6 months, and then every 3 months for the remainder of the study, or more frequently as clinically indicated Upon recurrence at 180 mg QD: Repeat above Hold until event is ≤ Grade 1, or has returned to baseline Resume at 120 mg QD Upon recurrence at 120 mg QD: Repeat above Hold until event is ≤ Grade 1, or has returned to baseline Resume at 90 mg QD Upon recurrence at 90 mg QD: Repeat above Hold until event is ≤ Grade 1, or has returned to baseline Resume at 60 mg QD Upon recurrence at 60 mg QD: Consider discontinuing treatment
Grade 3 (QTcF ≥ 501 ms on at least 2 separate ECGs)	First occurrence at any dose level: Hold treatment Perform serum electrolyte analysis (including potassium, calcium, and magnesium) and correct with supplements if below normal limits Review concomitant medications Repeat ECG as clinically indicated, but at least daily until QTcF returns to ≤ Grade 1 (480 ms) Resume at next lower dose level after recovery to ≤ Grade 1 If no contributing reason was identified for QTcF elevation, then weekly ECG monitoring is recommended for 4 weeks upon resumption of treatment, then monthly for 6 months, and then every 3 months for the remainder of the study, or more frequently as clinically indicated Upon recurrence at 120 mg QD: Repeat above Hold until event is ≤ Grade 1, or has returned to baseline Resume at 90 mg QD Upon recurrence at 90 mg QD: Repeat above Hold until event is ≤ Grade 1, or has returned to baseline Resume at 60 mg QD Upon recurrence at 60 mg QD: Consider discontinuing treatment
Grade 4 (QTc ≥501 or >60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Consider discontinuing treatment

Hematologic Toxicity	
Grade 1	Continue at current dose
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

*Apply these recommendations either after dose escalation was accomplished, or after dose reduction for Grade 3 or 4 toxicity was implemented resulting in no dose escalation.

13.1.4 Dose Modification and Management of Specific Treatment-related Adverse Events

Comprehensive assessments of any study drug-related AEs (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 to be associated with study drug administration, should be reported on the appropriate concomitant medication page of the patient's eCRF. The symptoms should be reported on the AE page.

13.1.4.1 Early Onset Pulmonary Syndrome

An early onset pulmonary syndrome consistent in some cases with pneumonitis occurred shortly after treatment initiation in 15% of patients who had received AP26113 at 180 mg QD, and possibly in a patient at 120 mg. The syndrome may include the acute onset of symptoms of dyspnea, cough, chest tightness, and fever. It has been observed after a single dose of AP26113 in patients. It is possible that patients with pre-existing pulmonary interstitial disease, including lymphangitic involvement by tumor, may be at increased risk. The syndrome is associated in more severe cases with hypoxia and chest CT findings of ground glass opacities consistent with pneumonitis, and in these cases constituted SAEs. However, in some patients, the symptoms resolved without drug interruption, dose modification, or specific intervention. This suggests that the pathogenesis and natural history of this condition may differ from later-onset pneumonitis, rarely observed with AP26113, but described with other TKIs. Nonetheless, investigators must be aware that this pneumonitis-like syndrome may present within 24 hours of initial dosing.

The occurrence of the early onset pneumonitis-like syndrome was not observed at doses of 90 mg, and was more common at higher doses, suggesting a relationship to initial dose. Similar pulmonary events have not been reported frequently after the first several days of treatment, at which time higher drug concentrations are attained in most patients as drug accumulates due to its long half-life. The timing and the reversibility of the early onset pulmonary syndrome suggest that if a low initial dose was tolerated, the dose could be escalated to a higher dose without an increased risk of developing such events. This is the rationale for a lead-in period at 90 mg QD for the first 7 days before escalation to 180 mg QD.

Early onset respiratory events, including but not limited to, dyspnea, hypoxia, dry cough, chest tightness, and presumptive lung infection (pneumonia) should be monitored and reported. Newly developed or worsening of pulmonary symptoms in the first week of study drug administration specifically with hypoxia and ground glass opacity in the chest CT indicative of interstitial lung disease or pneumonitis could suggest a relationship to AP26113. 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 AP26113 should be considered. Such pulmonary events of hypoxia and radiographic evidence of pneumonitis occurring in patients in Arm B within the first 7 days of initial treatment should be evaluated before dose escalation. Although the early onset syndrome has not been observed after dose escalation to 180 mg, it should also be considered in the period immediately following dose escalation from 90 mg to 180 mg.

The management of early onset pulmonary symptoms should include drug interruption, monitoring of oxygen saturation, and radiographic evaluation, with high dose corticosteroids, supplemental oxygen therapy, and empiric antibiotics as indicated. Dose modification should be accomplished according to the recommendations in Table 4 and Table 5. If the symptoms include documented hypoxia and/or radiologic evidence of interstitial or ground glass changes, or result in an SAE, the early onset condition should be treated according to Table 7.

13.1.4.2 Pneumonitis

Pneumonitis, including interstitial lung disease, occurring later in the course of therapy, is a known side effect of TKIs used in NSCLC. 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®, 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. In the phase 1/2 study of AP26113, one case of drug-related grade 3 pneumonitis occurred (at 240 mg) 7.5 months after the first dose of AP26113, out of a total of 91 patients treated.

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 O_2 saturation, and 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 potentially discontinuation is required, as presented in Table 7.

Table 7 AP26113 Dose Modification Recommendations for Treatment-related Pneumonitis

Toxicity Grade	Dose Modification for Arm A	Dose Modification for Arm B
Grade 1	Withhold the dose until pneumonitis returns to Grade 0 (baseline), then resume at the same dose. If pneumonitis recurs, permanently discontinue treatment	Withhold the dose until pneumonitis returns to Grade 0 (baseline), then resume at the same dose. If occurs during 7-day lead-in at 90 mg QD, withhold dose until pneumonitis returns to grade 0, 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. Resume at 60 mg QD. If pneumonitis recurs, permanently discontinue treatment.	Withhold the dose until pneumonitis returns to Grade 0. Resume at 120 mg QD. If occurs during 7-day lead-in at 90 mg QD, withhold 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.	Permanently discontinue treatment.
Grade 4	Permanently discontinue treatment.	Permanently discontinue treatment.

13.1.4.3 Nausea and Emesis

Treat with standard-of-care antiemetics. Prophylactic antiemetics may be used.

13.1.4.4 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 AP26113 or the symptom recurs. For grade ≥3 despite loperamide, treatment will be withheld until recovery to grade ≤1 (Table 6). Other medications and supportive care may be added according to the institution's standard of care.

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 (eg, chemotherapy, radiotherapy, immunotherapy, biologics). The information must be obtained from the patient's medical chart and recorded on the appropriate eCRF.

Palliation 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 SRS are allowed to continue study treatment after appropriate interruption, as determined by the investigator; 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 30 Days After Last Dose, 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 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, including SRS, used for palliative or symptomatic control of existing lesions, with appropriate treatment interruption at the discretion of the investigator);

2. Use of any other investigational drug or device;
3. 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;
4. 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 medical monitor at the earliest possible time to determine whether it is safe for the patient to continue treatment with AP26113.

13.4 Potential Drug Interactions

In vitro studies with human liver microsomes indicate that cytochrome 450 (CYP) 2C8 and CYP3A4 are involved in the human metabolism of AP26113. Medications and dietary (grapefruit-containing products) or herbal products (St John's Wort) that are strong inhibitors or inducers of P450 cytochromes, in particular, CYP2C8 or CYP3A4, should be avoided (see Appendix D).

AP26113 is not a reversible inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5, with IC_{50}s of >70 μM. AP26113 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 AP26113 are unlikely.

13.5 Treatment Compliance

Patients will be provided a diary card or equivalent where the date of study drug administration will be recorded and complete instructions will be provided with the Study Reference Manual. Patients who forget to take their dose should not make up the missed dose. Any missing doses must be recorded in an appropriate source record (eg, clinic chart), patient diary card, and study drug administration eCRF. Training of patients should be documented in the appropriate source record (eg, 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 accounted for 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 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

AP26113 drug product is supplied as film-coated tablets, which may contain either 30 mg, 90 mg or 180 mg of AP26113 active pharmaceutical ingredient. Other ingredients are typical pharmaceutical excipients (lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, hydrophobic 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. AP26113 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.

13.6.2 Preparation and Dispensing

The study pharmacist or designee at the site will be responsible for handling and dispensing study drug, 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 (30 mg), quantity dispensed with the corresponding lot number, 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 AP26113 is under 30°C. Do not refrigerate or freeze.

The investigator is responsible for ensuring that the study drug provided to the patient and returned from the patient are accounted for 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 AP26113 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 (ie, occurs after the first dose of study drug), is also an AE.

Adverse events include:

- Abnormal test findings
- Changes in physical exam 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
- Drug withdrawal
- Drug abuse
- Drug misuse
- Drug interactions
- Drug dependency, and
- Exposure in utero

14.1.2 Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms that are considered clinically significant in the opinion of the investigator.
- Test result requires additional diagnostic testing (other than merely repeating an abnormal test) or medical/surgical intervention.

- Test result leads to a change in study drug dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
- Test result is considered to be an AE by the investigator or sponsor.

14.1.3 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 or its designated representative.

14.1.4 Reporting Adverse Events

For all enrolled patients, AEs should be recorded on the eCRF beginning with signing of the informed consent form and concluding 30 days following the last dose of the assigned study treatment, or the investigator/patient decision to discontinue treatment, whichever occurs later.

AEs ongoing after the reporting period: Any ongoing AEs thought to be at least possibly study-drug related after this time should be followed and reported to the sponsor's medical monitor at least every 4 weeks until they resolve to baseline (or CTCAE grade ≤1), stabilize, or are considered to be chronic/irreversible. See Section 14.2.2 for reporting SAEs.

14.1.5 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.

14.1.6 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 investigational product 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

14.1.7 Expectedness

The expectedness of an SAE is assessed by the sponsor in the overall classification of SAEs for regulatory reportability. The Clinical 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 AP26113.

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 (ie, 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 (ie, 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 (eg, patient has no place to sleep)
- Protocol-specified admission during a clinical study (eg, for a procedure required by the study protocol)
- Optional admission not associated with a precipitating AE (eg, 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

Serious AEs require immediate notification by the investigator or designee to ARIAD Pharmacovigilance and Risk Management, or its designated representative, beginning from the time the patient provides informed consent (ie, prior to undergoing any study-related procedure and/or receiving investigational product), through and including 30 days after the last administration of study treatment, or the investigator/patient decision to discontinue treatment, whichever occurs later. Any SAE occurring any time after the reporting period must be promptly reported to ARIAD Pharmacovigilance and Risk Management or its designated

representative immediately after becoming aware of the SAE if a causal relationship to the investigational product is suspected. All SAEs ongoing 30 days or more after last dose of study drug is administered should be followed at least every 4 weeks until they resolve to baseline (or CTCAE grade ≤1), stabilize, or are considered to be chronic/irreversible.

Should the FDA or national regulatory authorities require that the sponsor submit additional event data, the investigator will be asked to provide those data to the sponsor in a timely fashion.

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 (eg, sex, age, or date of birth)
- Information on study drug (eg, 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

Appropriate diagnostic tests should be performed and therapeutic measures, as medically indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out until the event has resolved or is otherwise explained by the investigator. For all SAEs, the investigator is obligated to pursue and provide information to ARIAD in a timely manner. In addition, an investigator may be requested by ARIAD to obtain specific information in an expedited manner. This information may be more detailed than that captured on the AE form. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes such as concomitant medication and illnesses must be provided.

Required Follow-up for Serious Adverse Events

There should be routine follow-up through and including 30 days after the last administration of assigned study treatment 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 returns to baseline. The medical monitor may specify a longer period of time if required to assure the safety of the patient.

Sponsor Responsibility for Expedited Safety Reports

ARIAD 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 Institutional Review Board (IRB)/Ethics Committee (EC) will determine if 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 shall be reported to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited safety reports and/or in aggregate reports), by the sponsor or its designated representative.

14.3 Other Safety Issues

14.3.1 Pregnancy

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 (ie, results in a low failure rate when used consistently and correctly) during the dosing period and for a period of at least 4 months thereafter. 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. 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 ARIAD medical monitor of this event and record the pregnancy on a 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 must be collected for the female partners of any males who took study drug in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

14.3.2 Overdose

An overdose is defined as the accidental or intentional ingestion or infusing of any dose of study treatment that exceeds the dose described in the protocol. Overdoses are not considered AEs; however, all overdoses should be recorded on an 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. Overdoses do not need to be

recorded on the CRF; dosing information is recorded on the CRF. Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the patient. If necessary, appropriate medical intervention should be provided. At the signing of the ICF, each patient must be given the names and telephone numbers of study site staff for reporting AEs, medical emergencies, pregnancies, and overdoses. Monitor AEs as instructed in the Schedule of Events (Section 11.1) and as clinically indicated.

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 treatment administration/compliance, efficacy, safety, pharmacokinetic parameters, and genetic status. Data will also be displayed graphically, where appropriate. Two-sided confidence intervals for all parameters to be estimated will be constructed using a significance level of alpha=0.05, with the exception of the primary endpoint, which will be tested at a two-sided alpha level of 0.025 to adjust for the multiplicity of having two treatment arms tested (with two-sided 97.5% confidence intervals).

Although this is a randomized study, inference will be made on each arm separately, and any comparisons will be purely descriptive. The primary analysis is planned to be conducted when all ongoing patients have completed their Cycle 6 disease assessment.

15.2 Analysis Populations

Intention to Treat (ITT) Population – The ITT population includes all patients randomized to each regimen regardless of 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 treatment. This will include patients who have experienced failure of crizotinib but do not have a history of ALK status by the Vysis® FISH test at baseline regardless of the results of the subsequent Vysis® FISH test performed at that time, as patients may be treated before these results are available.

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. In particular, patients who have no history of an ALK rearrangement by the Vysis® FISH test at study entry and whose protocol-mandated test is negative for an ALK rearrangement will be excluded from the per-protocol analysis.

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 confirmed ORR, as assessed by the investigator, per RECIST v1.1.

15.3.2 Secondary Endpoints

Secondary endpoints of the study include:

1. Confirmed ORR, as assessed by a central IRC, per RECIST v1.1
2. CNS response (ORR and PFS, per RECIST v1.1, in patients who have active brain metastases)
3. Time to response
4. Duration of response
5. Time on treatment
6. Disease control rate (the percentage of patients with best response of CR, PR, or SD, per RECIST v1.1)
7. Progression free survival (PFS)
8. Overall survival (OS)
9. Safety and tolerability
10. Steady-state plasma level of AP26113 for use in population PK modeling
11. Patient-reported symptoms of lung cancer and HRQoL scores, assessed with the EORTC QLQ-C30 (v3.0)

15.3.3 Exploratory Endpoints

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15.4 Determination of Sample Size

This is a phase 2, multicenter, randomized, open-label study in patients with ALK-positive, locally advanced or metastatic NSCLC who were previously treated with crizotinib. This study is designed to determine the efficacy in patients treated with daily oral administration of AP26113 at a dose of 90 mg QD continuously or 90 mg QD for 7 days followed by escalation to 180 mg QD continuously. The primary endpoint of this phase 2 study is confirmed ORR assessed by the investigator using RECIST v1.1. The primary analysis of the primary endpoint in the ITT population will be conducted using exact two-sided 97.5% binomial confidence intervals for each regimen. For the purpose of this study, the uninteresting ORR is set at 20% and the alternative ORR is set at 35%. A sample size of at least 218 patients (109 per treatment regimen) will provide approximately 90% power to rule out an uninteresting rate of 20% when

the true rate is 35% or higher at two-sided alpha level of 0.025 using exact binomial test. The treatment regimen will be considered to have achieved the primary objective when ORR assessed by the investigator is shown to be significantly higher than 20% at a two-sided alpha level of 0.025 at final analysis for that regimen.

15.5 Efficacy Analysis

15.5.1 Definitions of Efficacy Endpoints

The primary endpoint, ORR assessed by the investigator, is defined as the proportion of the patients who are confirmed to have achieved CR or PR, per RECIST v1.1 (confirmed ≥4 weeks after initial response), after the initiation of study treatment in the ITT population.

Secondary efficacy endpoints for this study are defined as follows:

- Confirmed ORR assessed by IRC is defined as the proportion of the patients who are confirmed to have achieved CR or PR per IRC using RECIST v1.1 after the initiation of study treatment in the ITT population.
- CNS ORR is defined as the proportion of the patients who have achieved CR or PR in the CNS per RECIST v1.1 after the initiation of study treatment in randomized patients with active CNS metastases at enrollment.
- CNS PFS is defined as the time interval from the date of the first dose of the study treatment until the first date at which CNS disease progression is objectively documented, or death due to any cause, whichever occurs first, in randomized patients with active CNS metastases at enrollment. It will be censored for patients without documented CNS disease progression.
- Time to response is defined as the time interval from the date of the first dose of the study treatment until the initial observation of CR or PR.
- Duration of response is defined as the time interval from the time that the measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that the progressive disease is objectively documented.
- Time on treatment is defined as the time from the first to the last dose of AP26113.
- Disease control rate is defined as the proportion of randomized patients who have achieved CR, PR, or SD (in the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks) after the initiation of study treatment.
- PFS is defined as the time interval from the date of the first dose of the study treatment 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.
- OS is defined as the time interval from the date of the first dose of the study treatment 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.

- Unless otherwise stated, secondary efficacy endpoints will use investigator assessments with sensitivity analyses performed using the IRC assessments.
- Censoring for time-to-event efficacy endpoints will be detailed in the SAP.

15.5.2 Primary Efficacy Endpoint Analyses

The best response (CR, PR, SD, or PD) according to RECIST v1.1 will be derived for each eligible patient who receives at least one dose of study treatment. Patients with no measurable disease at baseline or no adequate post-baseline response assessment will be included as non-responders. The ORR is calculated as the proportion of randomized patients who are confirmed to have achieved CR or PR after the initiation of study treatment. Confirmed responses are those that persist on repeat imaging at least 4 weeks after initial response. Exact two-sided 97.5% confidence intervals for the ORR will be calculated based on the binomial distribution. The primary analysis will be performed on ORR assessed by the investigator among all the randomized patients. Best target lesion response will be displayed using a "waterfall" plot. Supportive sensitivity analyses will be performed for ORR assessed by the investigator in the per-protocol population and using all responses (including unconfirmed responses).

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15.5.3 Secondary Efficacy Endpoint Analyses

Confirmed ORR assessed by an IRC in the ITT population and the per-protocol population will be analyzed to assess the robustness of the primary analysis of the primary endpoint.

Disease control rate assessed by the investigator in the ITT population and the per-protocol population and the exact two-sided 95% binomial confidence intervals will be calculated.

For time-to-event efficacy endpoints, median values and two-sided 95% confidence intervals will be estimated using Kaplan-Meier method (Kaplan and Meier, 1958) in the ITT population. The PFS rates and OS rates at 12 and 24 months and the associated two-sided 95% confidence intervals will be computed. Time to response will be summarized only for responders using descriptive statistics.

In randomized patients with active CNS metastases at enrollment, CNS ORR assessed by the investigator and IRC and the exact two-sided 95% binomial confidence intervals will be calculated; median CNS PFS will be estimated using the Kaplan-Meier method.

15.5.4 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. 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, early death from malignant disease, early death from toxicity, early death because of other cause, or unknown (including no measureable 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 one dose of study treatment will be evaluated for safety. The incidence rates of treatment emergent adverse events (TEAEs), treatment related adverse events (TRAEs), and serious treatment emergent adverse events (SAEs) will be described, as identified with preferred terms and MedDRA system organ class (SOC). 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.

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Exposure to study treatment 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 ms, 480 ms, and 500 ms; and the proportion of treated patients with a maximum change in QTcF from baseline >30 ms and >60 ms.

15.7 HRQoL Data Analysis

For HRQoL measures, raw scores for multi-item scales will be calculated by averaging items within scales first. Raw scores will be summarized by time point with descriptive statistics for each scale. Raw scores for multi-item scales and single-item measures will be linearly transformed to obtain the score ranging from 0 to 100 according to EORTC QLQ-C30 (V3) Scoring Manual (Fayers et al, 2001). The global health status / QoL scale based upon *Q29* and *Q30* will be used as the overall summary measure. The HRQoL scores including the overall

summary measure will be summarized at baseline and by time point in evaluable patients. The changes from baseline over time will be analyzed using mixed effects models.

Missing items will be imputed as the average of the items which are present for a multi-item scale if at least half of the items from the scale have been answered. A missing single-item measure will not be imputed. Missing forms will not be imputed. Patients with missing baseline scores will be excluded from the analysis for a scale when the change from baseline is analyzed or the baseline score is used as a covariate.

15.8 Correlation Analyses of Tumor and Plasma Biomarkers with Efficacy and Safety

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15.9 Protocol Deviations/Violations

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

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 Clinical 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 legibility, 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,
- Disclosure of financial interests in ARIAD or ARIAD products (as defined in 21 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.

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/EC. The signed IRB/EC approval letter must identify the documents approved (ie, 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/EC. The sponsor will not ship clinical supplies until a signed approval

letter from the IRB/EC 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 your proposed informed consent document should be submitted to the sponsor for review and comment before submission to your IRB/EC. 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/EC. 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, as specified in the protocol. 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 in consultation with the Study Steering Committee.

17.4.2 Independent Review Committee

A central IRC will evaluate all images collected during the study for the secondary endpoint of confirmed ORR by IRC. An IRC 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 be responsible for periodic review of study data to evaluate the safety profile of AP26113, assess accumulating signals of efficacy, evaluate data quality, and 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 enrolled 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/EC, 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/EC 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 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, eCRFs, 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 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/EC 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/EC 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.clinicatrialsregister.eu/ [Accessed: 13 January 2014]).

The institution and principal investigator acknowledge that the study is multi-center 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 Multi-Center Publication has not been completed within one (1) year from the date of the completion, termination, or abandonment of the multi-center 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: 13 January 2014]

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. MedDRA v12.0.

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, eg, light house work, office work
2	Ambulatory and capable of all selfcare 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 (eg, "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 SPD

- 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 (eg, 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 (<10mm 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 (eg, 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: 13 January 2014]. 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: 13 January 2014] 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.

Table 1.1 Drugs Generally Accepted by the QTDrugs.org Advisory Board of the Arizona CERT to have a Known Risk of Causing Torsades de Pointes; Prohibited in this Study

Generic Name	Brand Name	Class/Clinical Use
Amiodarone	Cordarone®, Pacerone®, Nexterone®	Antiarrhythmic / abnormal heart rhythm
Arsenic trioxide	Trisenox®	Anticancer / Leukemia
Astemizole	Hismanal®	Antihistamine / Allergic rhinitis
Azithromycin	Zithromax®, Zmax®	Antibiotic / bacterial infection
Bepridil	Vascor®	Antianginal / heart pain
Chloroquine	Aralen®	Antimalarial / malaria infection
Chlorpromazine	Thorazine®, Largactil®, Megaphen®	Antipsychotic/ Antiemetic / schizophrenia/ nausea
Cisapride	Propulsid®	GI stimulant / heartburn
Citalopram	Celexa®	Antidepressant / depression
Clarithromycin	Biaxin®, Prevpac®	Antibiotic / bacterial infection
Cocaine	Cocaine	Local anesthetic / topical anesthetic
Disopyramide	Norpace®	Antiarrhythmic / abnormal heart rhythm

Dofetilide	Tikosyn®	Antiarrhythmic / abnormal heart rhythm
Domperidone	Motilium®, Motillium®, Motinorm Costi®, Nomit®	Antinausea / nausea
Dronedarone	Multaq®	Antiarrhythmic / atrial fibrillation
Droperidol	Inapsine®, Droleptan®, Dridol®, Xomolix®	Sedative; Antinausea / anesthesia adjunct, nausea
Erythromycin	Erythrocin®, E.E.S.®, Robimycin®, 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®, Tiloryth®	Antibiotic; GI stimulant / bacterial infection; increase GI motility
Escitalopram	Cipralex®, Lexapro®, Nexito®, Anxiset-E®, Exodus®, Esto®, Seroplex®, Elicea®, Lexamil®, Lexam®, Entact®, Losita®, Reposil®, Animaxen®, Esitalo®, Lexamil®	Antidepressant / major depression, anxiety disorder
Flecainide	Tambocor®, Almarytm®, Apocard®, Ecrinal®, Flécaine®	Antiarrhythmic / abnormal heart rhythm
Halofantrine	Halfan®	Antimalarial / malaria infection
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

Levomethadyl	Orlaam®	Opiate agonist / pain control, narcotic dependence
Mesoridazine	Serentil®	Antipsychotic / schizophrenia
Methadone	Dolophine®, Symoron®, Amidone®, Methadose®, Physeptone®, Heptadone®	Opiate agonist / pain control, narcotic dependence
Moxifloxacin	Avelox®, Avalox®, Avelon®	Antibiotic / bacterial infection
Ondansetron	Zofran®, Anset®, Ondemet®, Zuplenz®, Emetron®, Ondavell®, Emeset®, Ondisolv®, Setronax®	Somatostatin analog / nausea and vomiting
Pentamidine	Pentam®, NebuPent®	Anti-infective / pneumocystis pneumonia
Pimozide	Orap®	Antipsychotic / Tourette's tics
Probucol	Lorelco®	Antilipemic / Hypercholesterolemia
Procainamide	Pronestyl®, Procan®	Antiarrhythmic / abnormal heart rhythm
Quinidine	Quinaglute®, Duraquin®, Quinact®, Quinidex®, Cin-Quin®, Quinora®	Antiarrhythmic / abnormal heart rhythm
Sevoflurane	Ulane®, Sojourn®	Anesthetic, general / anesthesia
Sotalol	Betapace®, Sotalex®, Sotacor®	Antiarrhythmic / abnormal heart rhythm
Sparfloxacin	Zagam®	Antibiotic / bacterial infection
Terfenadine	Seldane®	Antihistamine / allergic rhinitis
Thioridazine	Mellaril®, Novoridazine®, Thioril®	Antipsychotic / schizophrenia
Vandetanib	Caprelsa®	Anticancer / thyroid cancer

AP26113-13-201 Protocol Amendment 3 - S Korea Clean

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Regulatory Affairs Approval	25-Aug-2015 16:40 GMT-04
	Medical Monitor Approval	25-Aug-2015 17:20 GMT-04