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

NCT Number: NCT01449461

Protocol Approve Date: 20 March 2017

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- Named persons or organizations associated with the study.
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CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1/2 Study of the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-Tumor Activity of the Oral ALK/EGFR Inhibitor AP26113
Protocol Number:	AP26113-11-101
Study Phase:	Phase 1/2
Product Name:	AP26113
IND Reference Number:	IND 110,935
EudraCT Number:	2011-005718-12
Sponsor:	ARIAD Pharmaceuticals, Inc. 125 Binney Street Cambridge, MA 01242 Telephone: +1 (617) 494-0400
Original Protocol Issue Date:	27 June 2011
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Amendment Number	Protocol Version Number	Date
	Version 1.0	27 June 2011
Amendment 1	Version 2.0	22 July 2011
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Amendment 5	Version 6.0	22 May 2013
Amendment 6	Version 7.0	20 December 2013
Amendment 7	Version 8.0	20 March 2017

PROTOCOL APPROVAL PAGE

Signatory*

PPD

**NOTE: 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.*

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)

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.

PPD

Date (dd-mmm-yyyy)

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PROTOCOL SYNOPSIS

Sponsor	ARIAD Pharmaceuticals, Inc. 125 Binney St. Cambridge, MA 01242
Study Treatment	AP26113
Study Title	A Phase 1/2 Study of the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-Tumor Activity of the Oral ALK/EGFR Inhibitor AP26113
Phase	Phase 1/2
Summary and Study Rationale	Specific genetic lesions that drive the proliferation of cancer cells, such as those causing activation of certain tyrosine kinases, render some cancers highly sensitive to therapeutic agents that inhibit the kinase. However, the efficacy of such agents is often limited by the development of mutations in the target kinase domain that confer resistance by reducing inhibitor binding. For example, the ABL kinase inhibitor imatinib has revolutionized treatment for patients with chronic myeloid leukemia (CML), whose disease is driven by an activated BCR-ABL fusion oncoprotein. Over time, however, development of mutations in the ABL kinase domain confers resistance in a substantial proportion of patients. The second-generation ABL inhibitors dasatinib and nilotinib, by virtue of being more potent inhibitors of ABL, demonstrate superior efficacy, and are able to overcome much of the mutation-based resistance exhibited by imatinib. More recently, genetic lesions in 2 other tyrosine kinases, anaplastic lymphoma kinase (ALK) and the epidermal growth factor receptor (EGFR) have been identified that show a similar pattern of sensitivity to first-generation inhibitors and susceptibility to mutation-based resistance. Activating gene rearrangements or mutations in ALK have been identified as driver mutations in some patients with non-small cell lung cancer (NSCLC), anaplastic large cell lymphoma (ALCL), diffuse large-cell lymphoma (DLCL), inflammatory myofibroblastic tumors (IMT), neuroblastoma, and other cancers. Crizotinib, an ALK kinase inhibitor, has demonstrated promising clinical activity in NSCLC, ALCL, and IMT patients harboring ALK translocations (Butrynski, 2010; Kwak, 2010; Gambacorti-Passerini, 2011). However, emerging data suggest that mutations in the kinase domain of ALK, including at the gatekeeper residue (L1196M), can confer resistance to crizotinib (Choi, 2010). Therefore, an ALK inhibitor that is more potent than crizotinib may be required to overcome such resistance.

	Activating mutations in EGFR have been identified in 10% to 20% of patients with NSCLC—the EGFR kinase inhibitors gefitinib and erlotinib have demonstrated activity in these patients. However, the clinical efficacy of gefitinib and erlotinib is ultimately limited by the development of resistance, such as by mutation in the EGFR kinase domain gatekeeper residue (T790M), which occurs in 50% of patients (Yun, 2008; Suda, 2010). Second-generation agents capable of inhibiting the T790M mutant form are in development, but can exhibit toxicity due to co-inhibition of native (endogenous) EGFR, suggesting that a T790M-selective agent will be required. To address limitations of existing inhibitors of ALK and EGFR, ARIAD is developing AP26113, a novel, synthetic, orally-active tyrosine kinase inhibitor (TKI). AP26113 potently inhibits activated forms of ALK and EGFR, as well as mutated resistant forms of both proteins, including the respective L1196M and T790M gatekeeper variants. Notably, AP26113 does not inhibit native EGFR. In addition, its spectrum of kinase inhibitory activity includes other targets potentially important in oncogenesis. In in vitro assays, AP26113 also inhibits the activity of ROS1, FAK, and CHK2 kinases. Based on the promising activity profile of AP26113 in vitro and in vivo, as well as its pharmacologic profile, this phase 1/2 clinical trial of the agent is the first assessment of AP26113 in patients. The trial will be conducted in 2 parts: a dose escalation phase, followed by an expansion phase. The patient population of the initial dose escalation phase of the trial will include patients with advanced malignancies, all histologies other than leukemia, refractory to available therapies or for whom no standard or available curative treatments exist. The objectives will be to determine the safety, tolerability, pharmacokinetic profile, and recommended phase 2 dose (RP2D) of orally administered AP26113 in these patients. The RP2D is the maximum tolerated dose (MTD) or less. An RP2D less than the MTD may be chosen if aspects of tolerability not encompassed by the MTD determination suggest utilizing a lower dose. The expansion phase will include 5 histologically and molecularly defined cohorts, with cohort 5 being limited to patients with active brain metastases. The dose and schedule for the expansion cohorts will be determined based on the RP2D and schedule determined in the dose escalation phase of the trial. The decision to open the expansion cohorts will be based on an assessment of safety and preliminary anti-tumor activity from the dose escalation cohort. The 5 expansion cohorts are as follows: 1. NSCLC patients with ALK rearrangements who are naive to prior ALK inhibitor therapy;

	2. NSCLC patients with ALK rearrangements who are resistant to crizotinib; 3. NSCLC patients who are resistant to 1 prior EGFR TKI and have a documented EGFR-T790M mutation following disease progression on the most recent EGFR TKI therapy; 4. Patients with any cancers with abnormalities in ALK or other AP26113 targets (examples include, but are not limited to, ALCL, DLCL, IMT, and other cancers with ALK abnormalities, or tumors with ROS1 fusions); 5. NSCLC patients with ALK rearrangements who are either naive or resistant to crizotinib and who have active brain metastases. The safety and tolerability of orally administered AP26113 will continue to be assessed in the expansion cohorts. However, the primary objective of the expansion component of the trial is to describe the preliminary efficacy of AP26113 in these patient populations. Overall response rate will be the primary endpoint in expansion cohorts 1-4, and CNS response rate will be the primary endpoint in expansion cohort 5.
Study Design	Open-label, multi-center, dose escalation study (3+3 design initial dose escalation cohort) with expansion into 5 cohorts (histologically and molecularly defined) after the RP2D is established.
Study Objectives	1. To determine the safety profile of orally administered AP26113 including identification of the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs). 2. To determine the RP2D of orally administered AP26113. 3. To examine the pharmacokinetic (PK) profile of AP26113. 4. To describe the preliminary anti-tumor activity of AP26113 in NSCLC with ALK gene rearrangement or mutated EGFR, and other cancers with abnormal targets. 5. CCI [redacted]
Study Endpoints	**Dose Escalation Component** Primary Endpoint: 1. RP2D of orally administered AP26113. Secondary Endpoints: 1. MTD of orally administered AP26113. 2. Safety, tolerability and DLTs of AP26113. 3. Plasma PK parameters of single-dose and steady state AP26113.

	Expansion Cohorts Primary Endpoint: 1. Overall response rate (using Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1). • For cohort 5: CNS response rate using RECIST. Secondary Endpoints: 1. Safety and tolerability of AP26113. 2. Plasma PK parameters. 3. Efficacy assessments include: best target lesion response; progression free survival (PFS); time to progression (TTP); time to treatment failure in patients who remain on study after RECIST progression, but who continue to benefit according to the treating investigator. Overall survival (OS) will also be measured for up to 2 years following the first dose of AP26113. • For cohort 5: additional efficacy assessments include: overall response rate using RECIST, CNS PFS, and extra CNS PFS. **Dose Escalation and Expansion Cohorts** CCI [redacted]
Diagnosis and Main Inclusion Criteria	Patients must meet all the criteria for the cohort for which their entry is proposed. Part 1: Dose escalation cohort (initial cohort):

1. Histologically confirmed advanced malignancies. All histologies except leukemia;
2. Refractory to available therapies or for whom no standard or available curative treatments exist;
3. Tumor tissue available for analysis. Patients with less tissue than required can be enrolled **only** with **prior** approval from the Sponsor.

Part 2: Expansion cohorts (5 additional cohorts):

1. Expansion cohort 1: NSCLC patients whose tumors exhibit ALK rearrangements and who have not been treated with previous ALK inhibitors:
    i. Histologically or cytologically confirmed NSCLC;
    ii. Tumor tissue available for analysis (see General Eligibility Criterion 1);
    iii. History of ALK rearrangement by FISH;
    iv. No prior ALK inhibitor therapy.
2. Expansion cohort 2: NSCLC patients whose tumors exhibit ALK rearrangements and who are resistant to crizotinib:
    i. Histologically or cytologically confirmed NSCLC;
    ii. Tumor tissue available for analysis (see General Eligibility Criterion 1);
    iii. History of ALK rearrangement by FISH;
    iv. Resistant to crizotinib (and have not received any other prior ALK inhibitor therapy).
3. Expansion cohort 3: NSCLC patients whose tumors exhibit an EGFR-T790M mutation and who are resistant to 1 prior EGFR TKI:
    i. Histologically or cytologically confirmed NSCLC;
    ii. Previous treatment with only 1 EGFR TKI for which the last administration was within 30 days of the initiation of AP26113;
    iii. Documented evidence of an EGFR-T790M mutation following disease progression on the most recent EGFR TKI therapy;
    iv. No intervening systemic therapy between

	cessation of the EGFR TKI and initiating AP26113; v. Tumor tissue available for analysis (see General Eligibility Criterion 1). 4. Expansion cohort 4: Patients with any cancers with abnormalities in ALK or other AP26113 targets. Examples include, but are not limited to, ALCL, DLCL, IMT, and other cancers with ALK abnormalities, or tumors with ROS1 fusions: i. Histologically confirmed lymphomas and other cancers, with the exception of leukemias; ii. Tumor tissue available for analysis (see General Eligibility Criterion 1). 5. Expansion cohort 5: NSCLC patients whose tumors exhibit ALK rearrangements and who have active, measurable brain metastases: i. Histologically or cytologically confirmed NSCLC; ii. Tumor tissue available for analysis (see General Eligibility Criterion 1); iii. History of ALK rearrangement by FISH; iv. Either crizotinib naive or resistant; v. Have at least one measurable brain lesion (≥ 10 mm by contrast enhanced, T1 weighted magnetic resonance imaging [cMRI]). Previously treated brain lesions by stereotactic radiosurgery (SRS) or surgical resection should not be included as a target or non-target lesion; vi. Previously untreated brain metastases or previously treated brain metastases with radiologically documented new or progressing brain lesions. Unequivocal progression of previously treated lesions (non-SRS and non-surgically treated lesions) at least 3 months after the last treatment; vii. Neurologically stable. Patients must be on a stable or decreasing dose of corticosteroids and/or have no requirement for anticonvulsants for 5 days prior to the baseline MRI and for 5 days prior to initiating AP26113.

General Eligibility Criteria

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

1. All patients must have tumor tissue available for analysis. If sufficient tissue is not available, patients must undergo a biopsy to obtain adequate samples. For patients in expansion cohorts 2, 3, and 5, for whom failure of prior therapy is specified (crizotinib for cohorts 2 and 5, one EGFR-TKI for cohort 3), tumor tissue must be available following failure of the prior therapy. Requirements are provided in Section 5.1. Patients with less tissue than required can be enrolled **only** with **prior** approval from the Sponsor.
2. Must have measurable disease by RECIST.
3. Male or female patients ≥ 18 years old.
4. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
5. Minimum life expectancy of 3 months or more.
6. Adequate renal and hepatic function as defined by the following criteria:
   i. Total serum bilirubin ≤ 2 x upper limit of normal (ULN);
   ii. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN (or ≤ 5 x ULN if liver function abnormalities are due to underlying malignancy);
   iii. Serum creatinine < 2 x ULN;
   iv. Serum albumin ≥ 2 g/dL.
7. Adequate bone marrow function as defined by the following criteria:
   i. Absolute neutrophil count (ANC) ≥ 1500/µL;
   ii. Platelets ≥ 75,000/µL;
   iii. Hemoglobin ≥ 9.0 g/dL.
8. Normal QT interval on screening electrocardiogram (ECG) evaluation, defined as QTcF of ≤ 450 ms in males or ≤ 470 ms in females.
9. For females of childbearing potential, a negative pregnancy test must be documented prior to enrollment.
10. Female patients who are of childbearing potential and fertile male patients must agree to use an effective form of contraception with their sexual partners throughout study

	participation. 11. Signed and dated informed consent indicating that the patient has been informed of all pertinent aspects of the study. 12. Willingness and ability to comply with scheduled visits and study procedures.
Main Exclusion Criteria	1. Received an investigational agent ≤ 14 days prior to initiating AP26113. 2. Received systemic anticancer therapy (including monoclonal antibodies and irreversible TKIs such as afatinib or dacomitinib) or radiation therapy ≤ 14 days prior to initiating AP26113. a. Except for a reversible EGFR TKI (ie, erlotinib or gefitinib) or crizotinib, which are allowed up to 72 hours prior to initiating AP26113, provided that the patient is free of treatment-related toxicity that might confound the safety evaluation of AP26113. 3. Received any prior agents targeted against ALK, with the exception of crizotinib, or received more than 1 prior EGFR TKI. a. Re-challenge with the same TKI is allowed. 4. Major surgery within 28 days prior to initiating AP26113. 5. Brain metastases that are neurologically unstable or require anticonvulsants or an increasing dose of corticosteroids. a. Patients with previously treated brain metastases without evidence of disease or recurrence are allowed for cohorts 1-4. b. Patients with evaluable but non-measurable, active brain lesions who otherwise meet the criteria for cohort 5 for CNS disease can be enrolled in other cohorts. 6. Significant uncontrolled or active cardiovascular disease, specifically including, but not restricted to: a. Myocardial infarction or unstable angina within 3 months prior to first dose of AP26113; b. Any history of congestive heart failure within 3 months prior to first dose of AP26113; c. History of clinically significant (as determined by the treating physician) atrial arrhythmia or any ventricular arrhythmia. 7. Uncontrolled hypertension (Diastolic blood pressure [BP]

	> 100 mm Hg; Systolic > 150 mm Hg). 8. Prolonged QTcF interval, or being treated with medications known to cause Torsades de Pointes (refer to Attachment 4). 9. History or presence of pulmonary interstitial disease or drug-related pneumonitis. 10. Ongoing or active infection. The requirement for intravenous (IV) antibiotics is considered active infection. 11. Known history of human immunodeficiency virus (HIV). Testing is not required in the absence of history. 12. Pregnant or breastfeeding. 13. Malabsorption syndrome or other gastrointestinal illness that could affect oral absorption of AP26113. 14. Any condition or illness that, in the opinion of the Investigator, would compromise patient safety or interfere with the evaluation of the safety of the drug. 15. Leptomeningeal carcinomatosis and spinal cord compression. In the case of suspected meningeal involvement, a negative lumbar puncture prior to study entry is required.
Approximate Number of Patients	Approximately 110 to 175 patients total study 1. Dose escalation cohort • Approximately 6 dose levels = 30 to 70 patients 2. Expansion cohorts • 1 = NSCLC ALK inhibitor naive = approximately 20 patients • 2 = NSCLC ALK inhibitor resistant = approximately 50 patients • 3 = NSCLC EGFR-T790M and resistant to 1 prior EGFR TKI = approximately 20 patients • 4 = Other cancers with ALK and/or ROS1 positivity = approximately 20 patients • 5 = ALK+ NSCLC with active brain metastases = approximately 25 patients
Approximate Duration of Patient Participation	The expected total duration of patient participation is approximately 2 years, including a 2- to 3-week screening period, an estimated average of 10 to 12 cycles (28 days each) of AP26113 in responding patients (participation for patients who do not respond will most likely be of shorter duration), and the 30-day after treatment discontinuation

	assessments. Overall survival (OS) will also be measured at least every 3 months, for up to 2 years following the first dose.
Approximate Duration of Study	The total estimated duration of the study is 4 years, including 24 months to accrue patients with 2 years for treatment and follow-up for the last patient. Patients who are still on study at 2 years will be allowed to receive study drug beyond 2 years until disease progression or they discontinue treatment for other reasons.
Approximate Number of Study Centers	Approximately 10 centers
Dosage and Administration	Based on preclinical 28-day toxicity data generated in rodents and non-human primates, the proposed starting dose of AP26113 in this phase 1/2 trial is 30 mg administered orally once daily. The dose escalation phase of this phase 1/2 trial will employ sequential dose escalation of oral AP26113 using a standard 3+3 design, starting at 30 mg administered orally once daily, and increasing in increments until the MTD is identified. The initial planned dose level cohorts are 30 mg, 60 mg, 90 mg, and 120 mg once daily oral doses of AP26113. Further dose escalation will involve increments of no more than 50% of the previous dose depending on safety findings. Multiple doses (eg, twice daily) may be administered daily based on PK findings (eg, half-life [$t_{1/2}$]) for the initial patients. The number of patients in each dose level cohort may vary depending on the events of the study, but cohorts will have a minimum of 3 patients enrolled. At each dose level, 3 patients will be enrolled initially and followed for 28 days. Increasing to the next dose level will depend on the safety findings of the previous cohort. If no DLTs are observed, the next higher cohort will begin enrollment. Expansion of a cohort from 3 to 6 patients will occur if 1 of 3 patients experiences a DLT at a given dose. Expansion may also occur at any dose to confirm safety observations. Standard definitions of DLT and MTD will be employed. The maximum administered dose in the trial will likely exceed the MTD. Intermediate doses between the MTD and the next lower dose may be explored. Schedules for single or multiple dosing of AP26113 in a given period may be explored depending on PK findings. Intra-patient dose escalation will be allowed according to the following scheme. All patients will have the option to increase dose while on study if the following conditions are met: 1) the patient tolerated his/her starting dose without a DLT and s/he remains on study without disease progression, 2) the Cycle 2 PK samples have been drawn per protocol, and 3) the proposed next dose level has been evaluated and it has been shown that it does not exceed the MTD.

Concomitant Treatment	Palliation and supportive care are permitted during the course of the trial for management of symptoms and underlying medical conditions that may develop during the study. The inclusion and exclusion criteria should be used to determine which medications a patient is allowed to be on at the time of screening and study entry. Once a patient has begun treatment, a condition may arise that requires the initiation of a new concomitant treatment. After a patient has begun the study, the addition of the following concurrent medications are prohibited: 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 Attachment 4). Medications that prolong the QT interval, but are not known to be associated with Torsades, should be avoided, but are not prohibited; 4. Herbal preparations or related over-the-counter preparations containing herbal ingredients; 5. Extensive surgery requiring in-patient care (patients may have an interruption in therapy for 14 days should emergency surgery be required). Patients should avoid using AP26113 in combination with other agents known to cause bradycardia (eg, beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin). The investigator or qualified designee should also educate patients not to start on any over-the-counter (OTC) medications, herbal or prescription medications that may affect heart rate, and to consult with the investigator prior initiating any therapy. Medications that are potent inhibitors or inducers of p450 cytochromes, in particular CYP2C8 and CYP3A4, should be avoided.
Safety Evaluation	Safety assessments will include physical and laboratory examinations, vital signs, and ECGs. Adverse events (AEs) will be graded according to the National Cancer Institute (of the United States) Common Terminology Criteria for Adverse Events (NCI CTCAE v 4.0; see Attachment 1). Periodic meetings with study investigators will be held to assess safety throughout the trial. All patients receiving at least 1 dose of AP26113 will be considered

	evaluable for safety. The 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. *Maximum Tolerated Dose (MTD)* The MTD is defined as the highest dose at which ≤ 1 of 6 evaluable patients experience a DLT within the first 28 days of treatment (end of cycle 1). Evaluable patients must complete at least 75% of their planned doses, unless missed doses are due to AEs. The cohort may be expanded to better define the safety profile for confirmation of the MTD. The maximum administered dose in the trial will likely exceed the MTD. *Dose-Limiting Toxicities (DLTs)* Standard AEs will be considered DLTs that count for the determination of the MTD of AP26113. A DLT is a drug-related toxicity that is observed to occur within the first 28 days of treatment (end of cycle 1) as defined below. Drug-related toxicities include any toxicity that is possibly, probably, or definitely drug-related. Toxicity grades will be defined by the NCI CTCAE v 4.0. DLTs are defined by the following: • Non-hematologic toxicities: i. Any grade ≥ 3 non-hematologic toxicity, with the exception of self-limiting or medically controllable toxicities (eg, nausea, vomiting, fatigue, electrolyte disturbances, hypersensitivity reactions) lasting < 3 days, and excluding alopecia. • Hematologic toxicities: i. Febrile neutropenia not related to underlying disease (fever, > 101°F [> 38.3°C]; ANC < 500); ii. Prolonged grade 4 neutropenia (> 7 days); iii. Neutropenic infection: ≥ grade 3 neutropenia with ≥ grade 3 infection; iv. Thrombocytopenia ≥ grade 3 with bleeding or grade 4 lasting ≥ 7 days. • Missed ≥ 25% of planned doses of AP26113 over 28 days due to treatment-related AEs in the first cycle.
QT Interval Evaluation	The following ECG assessments will be required. Triplicate ECGs at Cycle 1, Day 1 before the first dose of AP26113. Triplicate ECGs on Cycle 2, Day 1 (Day 29) prior to administration of the Cycle 2, Day 1 dose, and at 1, 2, 4, and 6 hours after dosing of AP26113. ECGs will be

	recorded electronically and will be evaluated centrally.
Pharmacokinetic Evaluation	Blood samples will be collected at specified time points (pre- and post-dosing) to assess the plasma pharmacokinetics of single-dose and steady-state AP26113, and its metabolite AP26123, in both the dose escalation and expansion cohorts. Pharmacokinetic parameters such as time of maximum concentration, maximum concentration, area under the concentration-time curve, and terminal half-life will be estimated where possible. For single-dose PK data, blood samples will be collected immediately prior to the first dose (time 0), and 0.5, 1, 2, 4 (± 10 minutes), 6, 8 (± 20 minutes), and 24 hours (± 60 minutes) after the first dose. The 24-hour sample will be collected prior to drug administration on Cycle 1, Day 2. Blood samples will also be collected prior to dosing on Cycle 1, Days 8, 15, and 22. For steady-state PK data, blood samples will also be obtained at the beginning of Cycle 2 when plasma concentrations of AP26113 are expected to have achieved steady state. Samples will be collected before and 0.5, 1, 2, 4 (± 10 minutes), 6, 8 (± 20 minutes), 24, and 48 hours (± 60 minutes) after administration of AP26113 on Cycle 2, Day 1. No drug will be administered on Cycle 2, Day 2. If multiple daily doses (eg, BID dosing) are employed, only the first dose on Cycle 2, Day 1 will be administered. The 48-hour sample will be collected before administration of the dose on Cycle 2, Day 3. A PK sample will also be collected pre-dose on Cycle 3, Day 1. PK evaluation will also be performed for the expansion cohorts to obtain cohort-specific single-dose and trough PK at the recommended dose established in the dose escalation phase of the trial. PK sampling time points will be the same as the sampling time points in the dose escalation phase; however, adjustments may be made based on the PK findings in the dose escalation phase.
Efficacy Evaluation	In the expansion cohorts, preliminary efficacy will be assessed by overall response rate (or CNS response rate for cohort 5) using RECIST (as determined by the investigator). Secondary measures will include: best target lesion response, PFS, TTP, and time to treatment failure in patients who remain on study after RECIST progression, but who continue to benefit according to the treating investigator. Overall survival (OS) will also be measured for up to 2 years following the first dose of AP26113. Additional secondary efficacy assessments for cohort 5 include overall response rate using RECIST, CNS PFS, and extra CNS PFS.
Molecular Genetic Evaluations	CCI [redacted]

	CCI [redacted]
Statistical Methods	Descriptive statistics and analyses will be provided for each dose level, and for patients combined across dose levels where applicable. All patients who receive at least one (1) dose of AP26113 will be included in the analysis of safety data. For the expansion cohorts, preliminary estimates of clinical activity including response rate, PFS, TTP and best target lesion response will be determined. When appropriate, data from patients in the expansion cohorts will be summarized together with data from patients in the dose escalation phase. **Pharmacokinetic Analysis** Parameters: maximum concentration (C_{max}), time of maximum concentration (T_{max}), area under the curve (AUC; over the first 24 hours), and drug elimination half-life ($T_{1/2}$), will be estimated from plasma concentration data. The geometric mean and 95% confidence intervals (CIs) will be reported. Accumulation for C_{max}, and AUC will be estimated from plasma concentration levels on Cycle 1, Day 1 (Day 1) and Cycle 2, Day 1 (Day 29), using the geometric mean ratio and 95% CI. Dose linearity for C_{max} and AUC will be assessed using regression methods. **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 one on-drug QTcF value > 450 ms, 480 ms, and 500 ms; proportion of treated patients with a maximum change in QTcF from baseline > 30 ms and > 60 ms. The Fridericia correction (QTcF) will be used throughout. QTcF change from baseline and blood concentration will be analyzed using mixed effects models.
Rationale for Number of Patients	The purpose of this phase 1/2 trial is to determine the RP2D, MTD, safety, tolerability, and preliminary efficacy of oral AP26113 in patients with advanced malignancies other than leukemia. The sample size is determined based on clinical rather than statistical considerations. The number of patients in this trial is consistent with phase 1 dose finding studies; the histologically and molecularly defined expansion cohorts will facilitate obtaining preliminary estimates of clinical activity. With

	this design, the estimate of the rate of DLT at the MTD is in the range of 0.17 to 0.26. The estimate of the rate of DLT at the highest dose, which is 1 step above the MTD, is 0.33 (Ting, 2006).

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LIST OF ABBREVIATIONS

Abbreviation	Term
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ARIAD	ARIAD Pharmaceuticals, Inc.
AST	aspartate aminotransferase
AUC	area under the curve
ß-HCG	beta-human chorionic gonadotropin
BP	blood pressure; blast phase
BUN	blood urea nitrogen
CBC	complete blood count
cDNA	complementary deoxyribonucleic acid
cGMP	current Good Manufacturing Practice
CI	confidence interval
C_{max}	maximum concentration
CML	chronic myeloid leukemia
CNS	central nervous system
CPK	creatine phosphokinase
CR	complete response
CT	computed tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DDI	drug-drug interaction
DLCL	diffuse large-cell lymphoma
DLT	dose-limiting toxicity
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDTA	ethylenediaminetetraacetic acid
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
FFPE	Fixed-formalin paraffin-embedded
FISH	Fluorescence In Situ Hybridization
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HDPE	high density polyethylene
HIV	human immunodeficiency virus
HPFB	Canadian Health Products and Food Branch
IC50	50% inhibitory concentration

Abbreviation	Term
IND	Investigational New Drug
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (formerly known as International Conference on Harmonisation)
ICJME	International Committee of Medical Journal Editors
IMT	inflammatory myofibroblastic tumors
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	intravenous
LD_{50}	lethal dose, 50%; dose required to kill half of the tested population
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
ms	millisecond
MTD	maximum tolerated dose
NCI	National Cancer Institute (of the United States)
NCI CTCAE, v.4	NCI Common Terminology Criteria for Adverse Events, version 4.0
NSCLC	non-small cell lung cancer
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PDGFR	platelet-derived growth factor receptor
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
QD	every day
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
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SD	standard deviation, stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SRS	stereotactic radiosurgery
STD_{10}	dose that is severely toxic to 10% of tested rodents
$t_{1/2}$	half-life
TGA	Australian Therapeutic Goods Administration
TKI	tyrosine kinase inhibitor
T_{max}	time of maximum concentration
TTP	time-to-progression

Abbreviation	Term
ULN	upper limit of normal

DEFINITIONS OF TERMS

Term	Definition
Active Study Period	The *Active Study Period* for a patient begins with administration of the first dose of study drug and continues through 30 days following discontinuation of study drug.
Suspected Adverse Reaction	A *Suspected Adverse Reaction* is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of Investigational New Drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.
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	The *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.
30 Days After End of Treatment	At *30 Days After End of Treatment*, a patient completes all post-treatment discontinuation assessments.
End of Trial	The *End of Trial* (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.

Term	Definition
Follow-up Period	The *Follow-up Period* for a patient begins after the last completed assessment during the active study period 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.
On-Study Period	The *On-Study Period* for a patient begins with the signing of the informed consent form and concludes 30 days following the last dose of study drug.
Patient	Throughout this document the term *Patient* refers to a patient in this clinical research study.
QTcF	For the purposes of this study, the corrected (Fridericia) QT interval is calculated using the following formula: *QTcF* = QT interval/3√RR interval.
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), the Good Clinical Practice: Consolidated Guideline (Canada), the International Conference on Harmonisation Guideline for Good Clinical Practice, the Therapeutic Goods Administration Annotated International Conference on Harmonisation Guidelines (Australia), 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 appropriate health and regulatory agencies. These may be international, national, or local and may include but not be limited to the Australian Therapeutic Goods Administration (TGA), the Canadian Health Products and Food Branch (HPFB), the 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 appropriate research departments within ARIAD Pharmaceuticals, Inc., or its designee.

Term	Definition
Study Administrative Manual	In the context of this study, *Study Administrative Manual* is a general term for the information provided to sites on technical aspects of the trial.
Study Drug	A *Study Drug* is any drug, device, biological agent, or comparator (including placebo) used in the Sponsor's clinical research and development studies. 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.

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1 INTRODUCTION

1.1 Background

Specific genetic lesions that drive the proliferation of cancer cells, such as those causing activation of certain tyrosine kinases, render some cancers highly sensitive to therapeutic agents that inhibit the kinase. However, the efficacy of such agents is often limited by the development of mutations in the target kinase domain that confer resistance by reducing inhibitor binding. For example, the ABL kinase inhibitor imatinib has revolutionized treatment for patients with chronic myeloid leukemia (CML), whose disease is driven by an activated BCR-ABL fusion oncoprotein. Over time, however, development of mutations in the ABL kinase domain confers resistance in a substantial proportion of patients. The second-generation ABL inhibitors dasatinib and nilotinib, by virtue of being more potent inhibitors of ABL, demonstrate superior efficacy, and are able to overcome much of the mutation-based resistance exhibited by imatinib. More recently, genetic lesions in 2 other tyrosine kinases, anaplastic lymphoma kinase (ALK) and the epidermal growth factor receptor (EGFR) have been identified that show a similar pattern of sensitivity to first-generation inhibitors and susceptibility to mutation-based resistance.

Activating gene rearrangements or mutations in ALK have been identified as driver mutations in some patients with non-small cell lung cancer (NSCLC), anaplastic large cell lymphoma (ALCL), diffuse large-cell lymphoma (DLCL), inflammatory myofibroblastic tumors (IMT), neuroblastoma, and other cancers. Crizotinib, an ALK kinase inhibitor, has demonstrated promising clinical activity in NSCLC, ALCL, and IMT patients harboring ALK translocations (Butrynski, 2010; Kwak, 2010; Gambacorti-Passerini, 2011). However, emerging data suggest that mutations in the kinase domain of ALK, including at the gatekeeper residue (L1196M), can confer resistance to crizotinib (Choi, 2010). Therefore, an ALK inhibitor that is more potent than crizotinib may be required to overcome such resistance.

Activating mutations in EGFR have been identified in 10% to 20% of patients with NSCLC—the EGFR kinase inhibitors gefitinib and erlotinib have demonstrated activity in these patients. However, the clinical efficacy of gefitinib and erlotinib is ultimately limited by the development of resistance, such as by mutation in the EGFR kinase domain gatekeeper residue (T790M), which occurs in 50% of patients (Yun, 2008; Suda, 2010). Second-generation agents capable of inhibiting the T790M mutant form are in development, but can exhibit toxicity due to co-inhibition of native (endogenous) EGFR, suggesting that a T790M-selective agent will be required.

1.2 AP26113

AP26113 is a novel, synthetic, orally-active tyrosine kinase inhibitor (TKI), discovered and developed by ARIAD Pharmaceuticals Inc (the Sponsor). AP26113 will be developed in cancers that carry molecularly defined targets against which the agent is shown to have activity.

1.2.1 Preclinical Pharmacology

A series of in vitro and in vivo studies have been performed to characterize the pharmacodynamic profile of AP26113. These studies have demonstrated that the compound potently inhibits activated variants of ALK and EGFR such as EML4-ALK and EGFR-L858R. Moreover, AP26113 potently inhibits variants of ALK and EGFR that contain additional

mutations, including the L1196M and T790M gatekeeper mutations in ALK and EGFR, respectively, which have been shown to confer resistance to first-generation agents. AP26113 does not inhibit the activity of native EGFR, which has been associated with toxicities in patients. In addition, its spectrum of kinase inhibitory activity includes other targets potentially important in oncogenesis, including ROS1, FAK, and CHK2 kinases. Overall, the data establish that AP26113 has a promising profile as an anti-tumor agent and provide a strong rationale for moving forward with a clinical development program in cancer patients.

1.2.2 Preclinical Absorption, Distribution, Metabolism and Excretion (ADME)

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1.2.3 Preclinical Toxicology

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1.2.4 Starting Dose Rationale

The rationale for selecting the starting dose of AP26113 follows the guidance of an acceptable method for selecting the first dose of non-specific cytotoxic agents for a first-in-human trial in cancer patients (DeGeorge et al. 1998). This guidance recommends that the first-in-human trial begin with a dose that is 1/10 of the dose that causes severe toxicity (or death) in 10% of tested rodents (STD_{10}) on a mg/m^2 basis, provided that this dose level is shown to be tolerated in a non-rodent species. The STD_{10} of AP26113 in the 28-day dose regimen in rats is between 30 mg/kg/day (180 mg/m^2/day; 2% mortality) and 60 mg/kg/day (360 mg/m^2/day; 48% mortality). Based on these observations, the 30 mg/kg/day (180 mg/m^2/day) dose level, rather than a calculated STD_{10}, was used to determine an acceptable phase 1/2 clinical trial starting dose. Assuming human patients have a body surface area of 1.7 m^2, the 180 mg/ m^2/day dose in rats corresponds to 306 mg/day in humans. Based on the rule of 1/10 of the STD_{10} in mg/m^2 in

rodents, the starting dose in humans would be somewhat higher than 30 mg/day. Therefore, the selected initial dose of 30 mg/day (approximately 18 mg/m^2) represents a conservative and reasonably safe starting dose for the phase 1/2 clinical trial. In addition, this 30 mg/day dose is 5 times lower than the well tolerated dose of 90 mg/m^2/day (7.5 mg/kg/day) in the 28-day study in cynomolgus monkeys.

1.2.5 Clinical

There is no previous investigational or marketed product human experience with AP26113.

1.3 Study Rationale

To address limitations of existing inhibitors of ALK and EGFR, initial development focus for AP26113 will be in NSCLC with ALK gene rearrangements or EGFR gene activating and resistance mutations. AP26113 potently inhibits activated forms of ALK and EGFR, as well as mutated resistant forms of both proteins, including the respective L1196M and T790M gatekeeper variants. Notably, AP26113 does not inhibit native EGFR. In addition, its spectrum of kinase inhibitory activity includes other targets potentially important in oncogenesis. In in vitro assays, AP26113 also inhibits the activity of ROS1, FAK, and CHK2 kinases.

Based on the promising activity profile of AP26113 in vitro and in vivo, as well as its pharmacologic profile, this phase 1/2 clinical trial of the agent will be conducted in 2 parts: a dose escalation phase, followed by an expansion phase. The dose escalation phase will establish the safety, tolerability, and pharmacokinetic profile of AP26113, along with a recommended phase 2 dose (RP2D) and schedule of orally administered AP26113 for use in the expansion phase. The expansion phase will include 5 histologically and molecularly defined cohorts based on the known preclinical activity profile of AP26113, with emphasis on its ALK and EGFR inhibitory properties in the NSCLC setting.

Activity of AP26113 in patients with brain metastases is an important consideration for this therapy, given the critical unmet medical need CNS progression represents in patients treated with crizotinib (Camidge et al., 2012). Patients with brain metastases from NSCLC typically do not respond to crizotinib due to low penetration of the drug into the CNS (Camidge et al., 2012). Furthermore, prognosis for these patients is poor (survival of less than one year). Preliminary clinical CNS activity has been observed in patients with ALK+ disease with brain metastases in the phase 1 portion of this study. Thus, the fifth cohort will assess AP26113 activity in ALK+ NSCLC patients with active, measurable brain metastases.

2 STUDY OBJECTIVES

The objectives of this study are:

1. To determine the safety profile of orally administered AP26113 including identification of the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs).
2. To determine the RP2D of orally administered AP26113.
3. To examine the pharmacokinetic (PK) profile of AP26113.
4. To describe the preliminary anti-tumor activity of AP26113 in NSCLC with ALK gene rearrangement or mutant EGFR activity, and other cancers with abnormal targets.

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3 STUDY DESIGN

3.1 Overall Study Design and Plan

This is an open-label, multi-center, dose escalation study (3+3 design initial dose escalation cohort) with expansion into 5 cohorts (histologically and molecularly defined) after the RP2D is established. Figure 1 presents an illustration of the study design.

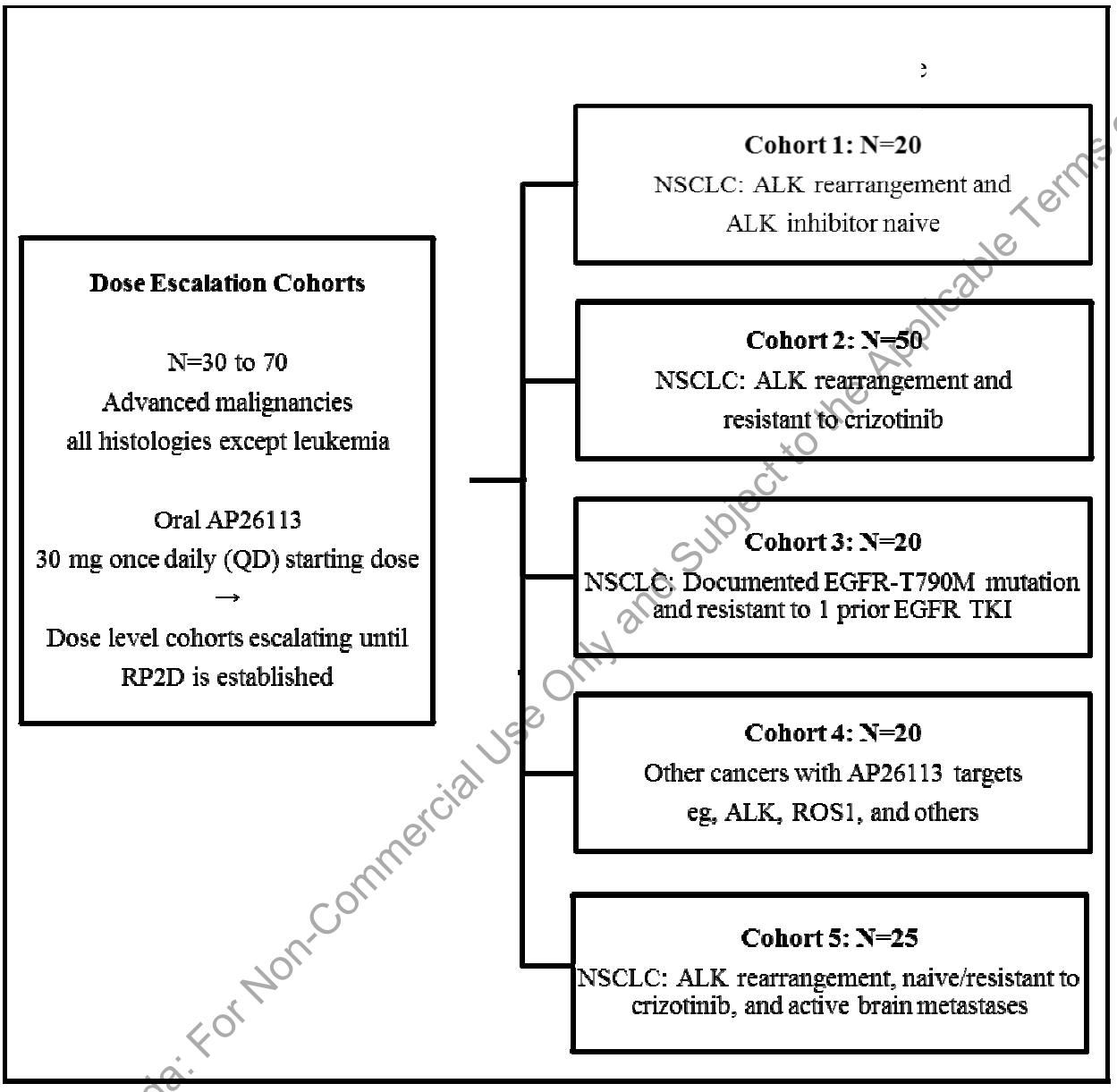
The patient population of the initial dose escalation phase of the trial will include patients with advanced malignancies, all histologies other than leukemia, refractory to available therapies or for whom no standard or available curative treatments exist. The objectives will be to determine the safety, tolerability, pharmacokinetic profile, and the RP2D of orally administered AP26113 in these patients. The RP2D is the maximum tolerated dose (MTD) or less. An RP2D less than the MTD may be chosen if aspects of tolerability not encompassed by the MTD determination suggest utilizing a lower dose.

The expansion phase will include 5 additional histologically and molecularly defined cohorts, with cohort 5 being limited to patients with active brain metastases. The dose and schedule for the expansion cohorts will be determined based on the RP2D and schedule determined in the dose escalation phase of the trial. The decision to open the expansion cohorts will be based on an assessment of safety and preliminary anti-tumor activity from the dose escalation cohort. The 5 expansion cohorts are as follows:

1. NSCLC patients with ALK rearrangements who are naive to prior ALK inhibitor therapy.
2. NSCLC patients with ALK rearrangements who are resistant to crizotinib.
3. NSCLC patients who are resistant to 1 prior EGFR TKI and have a documented EGFR-T790M mutation following disease progression on the most recent EGFR TKI therapy.
4. Patients with any cancers with abnormalities in ALK or other AP26113 targets (examples include, but are not limited to, ALCL, DLCL, IMT, and other cancers with ALK abnormalities, or tumors with ROS1 fusions).
5. NSCLC patients with ALK rearrangements who are either naive or resistant to crizotinib and who have active brain metastases.

The safety and tolerability of orally administered AP26113 will continue to be assessed in the expansion cohorts. However, the primary objective of the expansion component of the trial is to describe the preliminary efficacy of AP26113 in these patient populations. Overall response rate will be the primary endpoint in expansion cohorts 1-4, and CNS response rate will be the primary endpoint in expansion cohort 5.

Figure 1 **Schematic of AP26113 Phase 1/2 Trial Design – Dose Escalation and Expansion Phases**



4 SELECTION OF STUDY POPULATION

An estimated 135 to 175 patients are anticipated to enroll at approximately 10 centers, including approximately 30 to 70 patients in the dose escalation part of the study, and approximately 20 patients each in expansion cohorts 1, 3, and 4; 50 patients in cohort 2; and 25 patients in cohort 5.

4.1 Inclusion Criteria

4.1.1 Cohort Eligibility Criteria

Patients must meet all the criteria for the cohort for which their entry is proposed.

Part 1: Dose escalation cohort (initial cohort):

1. Histologically confirmed advanced malignancies. All histologies except leukemia;
2. Refractory to available therapies or for whom no standard or available curative treatments exist;
3. Tumor tissue available for analysis. Patients with less tissue than required can be enrolled **only** with **prior** approval from the Sponsor.

Part 2: Expansion cohorts (5 additional cohorts)

1. Expansion cohort 1: NSCLC patients whose tumors exhibit ALK rearrangements and who have not been treated with previous ALK inhibitors:
    i. Histologically or cytologically confirmed NSCLC;
    ii. Tumor tissue available for analysis (see General Eligibility Criterion 1);
    iii. History of ALK rearrangement by fluorescence in situ hybridization (FISH);
    iv. No prior ALK inhibitor therapy.
2. Expansion cohort 2: NSCLC patients whose tumors exhibit ALK rearrangements and who are resistant to crizotinib:
    i. Histologically or cytologically confirmed NSCLC;
    ii. Tumor tissue available for analysis (see General Eligibility Criterion 1);
    iii. History of ALK rearrangement by FISH;
    iv. Resistant to crizotinib (and have not received any other prior ALK inhibitor therapy).
3. Expansion cohort 3: NSCLC patients whose tumors exhibit an EGFR-T790M mutation and who are resistant to 1 prior EGFR TKI:
    i. Histologically or cytologically confirmed NSCLC;
    ii. Previous treatment with only 1 EGFR TKI for which the last administration was within 30 days of the initiation of AP26113;
    iii. Documented evidence of an EGFR-T790M mutation following disease progression on the most recent EGFR TKI therapy;
    iv. No intervening systemic therapy between cessation of the EGFR TKI and initiating AP26113;
    v. Tumor tissue available for analysis (see General Eligibility Criterion 1).

4. Expansion cohort 4: Patients with any cancers with abnormalities in ALK or other AP26113 targets. Examples include, but are not limited to, ALCL, DLCL, IMT, and other cancers with ALK abnormalities, or tumors with ROS1 fusions:
    i. Histologically confirmed lymphomas and other cancers, with the exception of leukemias;
    ii. Tumor tissue available for analysis (see General Eligibility Criterion 1).
5. Expansion cohort 5: NSCLC patients whose tumors exhibit ALK rearrangements and who have active, measurable brain metastases:
    i. Histologically or cytologically confirmed NSCLC;
    ii. Tumor tissue available for analysis (see General Eligibility Criterion 1);
    iii. History of ALK rearrangement by FISH;
    iv. Either crizotinib naive or resistant;
    v. Have at least one measurable brain lesion (≥ 10 mm by contrast enhanced, T1 weighted magnetic resonance imaging [cMRI]). Previously treated brain lesions by stereotactic radiosurgery (SRS) or surgical resection should not be included as a target or non-target lesion;
    vi. Previously untreated brain metastases or previously treated brain metastases with radiologically documented new or progressing brain lesions. Unequivocal progression of previously treated lesions (non-SRS and non-surgically treated lesions) at least 3 months after the last treatment;
    vii. Neurologically stable. Patients must be on a stable or decreasing dose of corticosteroids and/or have no requirement for anticonvulsants for 5 days prior to the baseline MRI and for 5 days prior to initiating AP26113.

4.1.2 General Eligibility Criteria

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

1. All patients must have tumor tissue available for analysis. If sufficient tissue is not available, patients must undergo a biopsy to obtain adequate samples. For patients in expansion cohorts 2, 3, and 5, for whom failure of prior therapy is specified (crizotinib for cohorts 2 and 5, one EFGR-TKI for cohort 3), tumor tissue must be available following failure of the prior therapy. Requirements are provided in Section 5.1. Patients with less tissue than required can be enrolled **only** with **prior** approval from the Sponsor.
2. Must have measurable disease by RECIST.
3. Male or female patients ≥ 18 years old.
4. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
5. Minimum life expectancy of 3 months or more.
6. Adequate renal and hepatic function as defined by the following criteria:

i. Total serum bilirubin ≤ 2 x upper limit of normal (ULN);

ii. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN (or ≤ 5 x ULN if liver function abnormalities are due to underlying malignancy);

iii. Serum creatinine < 2 x ULN;

iv. Serum albumin ≥ 2 g/dL.

7. Adequate bone marrow function as defined by the following criteria:

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

ii. Platelets ≥ 75,000/μL;

iii. Hemoglobin ≥ 9.0 g/dL.

8. Normal QT interval on screening electrocardiogram (ECG) evaluation, defined as QTcF of ≤ 450 ms in males or ≤ 470 ms in females.

9. For females of childbearing potential, a negative pregnancy test must be documented prior to enrollment.

10. Female patients who are of childbearing potential and fertile male patients must agree to use an effective form of contraception with their sexual partners throughout study participation.

11. Signed and dated informed consent indicating that the patient has been informed of all pertinent aspects of the study.

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

4.2 Exclusion Criteria

Patients are not eligible for participation in the study if they meet or have any of the following exclusion criteria:

1. Received an investigational agent ≤ 14 days prior to initiating AP26113.

2. Received systemic anticancer therapy (including monoclonal antibodies and irreversible TKIs such as afatinib or dacomitinib) or radiation therapy ≤ 14 days prior to initiating AP26113.

   a. Except for a reversible TKI (ie, erlotinib or gefitinib) or crizotinib, which are allowed up to 72 hours prior to initiating AP26113, provided that the patient is free of treatment-related toxicity that might confound the safety evaluation of AP26113.

3. Received any prior agents targeted against ALK, with the exception of crizotinib, or received more than 1 prior EGFR TKI.

   a. Re-challenge with the same TKI is allowed.

4. Major surgery within 28 days prior to initiating AP26113.

5. Brain metastases that are neurologically unstable or require anticonvulsants or an increasing dose of corticosteroids.
    a. Patients with previously treated brain metastases without evidence of disease or recurrence are allowed for cohorts 1-4.
    b. Patients with evaluable but non-measurable, active brain lesions who otherwise meet the criteria for cohort 5 for CNS disease can be enrolled in other cohorts.
6. Significant uncontrolled or active cardiovascular disease, specifically including, but not restricted to:
    a. Myocardial infarction or unstable angina within 3 months prior to first dose of AP26113;
    b. Any history of congestive heart failure within 3 months prior to first dose of AP26113;
    c. History of clinically significant (as determined by the treating physician) atrial arrhythmia or any ventricular arrhythmia.
7. Uncontrolled hypertension (Diastolic blood pressure [BP] > 100 mm Hg; Systolic > 150 mm Hg).
8. Prolonged QTcF interval, or being treated with medications known to cause Torsades de Pointes (refer to Attachment 4).
9. History or presence of pulmonary interstitial disease or drug-related pneumonitis.
10. Ongoing or active infection. The requirement for IV antibiotics is considered active infection.
11. Known history of human immunodeficiency virus (HIV). Testing is not required in the absence of history.
12. Pregnant or breastfeeding.
13. Malabsorption syndrome or other gastrointestinal illness that could affect oral absorption of AP26113.
14. Any condition or illness that, in the opinion of the Investigator, would compromise patient safety or interfere with the evaluation of the safety of the drug.
15. Leptomeningeal carcinomatosis and spinal cord compression. In the case of suspected meningeal involvement, a negative lumbar puncture prior to study entry is required.

5 STUDY PROCEDURES

The *on-study period* begins with the signing of the informed consent form and ends 30 days following the last dose of study drug. 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 *active study period* begins with administration of the first dose of AP26113 and continues through 30 days following discontinuation of AP26113.

The *follow-up period* begins after the last completed assessment during the active study period and continues until patient contact discontinues.

5.1 Study Procedure Descriptions

See the Schedule of Events for the required assessments at each visit. The following list describes the procedures/tests required for this study.

1. **Informed consent**

   Informed consent, documented by a signed consent form, must be obtained prior to any screening activities not otherwise part of the patient's care.

2. **Demographics**

   Demographic information consists of the patient's age, gender, race, and ethnicity (as allowed by local law and regulations).

3. **Medical and Surgical History**

   Medical and surgical history includes diagnoses, procedures, smoking history, medical and surgical treatments, and current medications.

4. **Prior Cancer Therapy**

   Prior cancer therapy history consists of the specific oncologic regimens a patient has received, the dates of the regimen and the best response to the regimen, and the reason for failure or intolerance to each regimen. Stem cell transplant or experimental or investigational therapy history must also be recorded.

5. **Diagnosis**

   The initial cancer diagnosis and the current cancer diagnosis at the time of screening (if different), along with dates of diagnosis and tumor histology, need to be recorded.

6. **Mutation Status**

   Regarding current and past ALK and EGFR 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 IHC, ALK point mutations, activating or resistance mutations or deletions of EGFR, and other mutations). For patients entering cohort 3, documentation of the EGFR-T790M mutation is required, following progression on the most recent EGFR-TKI treatment course.

7. **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. 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.

8. **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.

9. **Pulse Oximetry**

Pulse oximetry assessments will be taken at screening, prior to the first dose, and approximately 4 and 24 hours after the first dose. Pulse oximetry will only be performed on patients enrolled in the dose escalation portion (phase 1) of the study.

10. **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 Attachment 2.

11. **Hematology**

Hematology measurements include complete blood count (CBC) with differential and platelet count.

12. **Serum Chemistry**

Serum chemistry (fasting) consists of a peripheral blood draw with the following assessments: sodium, potassium, chloride, bicarbonate (or total carbon dioxide [CO_2]), blood urea nitrogen (BUN, or urea), albumin and total protein, creatinine, total bilirubin (both direct and indirect), ALT (SGPT), AST (SGOT), alkaline phosphatase, magnesium, phosphorous, calcium, lactate dehydrogenase (LDH), uric acid, amylase and lipase, creatine phosphokinase (CPK), and glucose. If non-fasting serum chemistry blood draws are taken, this should be noted, along with the time the patient last ate and the reason the patient did not fast.

13. **Urinalysis**

Urinalysis will include pH, specific gravity, protein, ketones, glucose, urobilinogen, and occult blood.

14. **Insulin**

Serum insulin and glucose should be measured concurrently. If non-fasting insulin blood draws are taken, this should be noted, along with the time the patient last ate and the reason the patient did not fast.

15. **Testosterone Level (males only)**

In male patients, serum testosterone should be measured at Cycle 1, Day 1 and per the Schedule of Events throughout the study.

16. **Thyroid-Stimulating Hormone**

Thyroid-stimulating hormone should be measured at Cycle 1, Day 1 and per the Schedule of Events throughout the study.

17. **Prothrombin Time (PT) and Partial Thromboplastin Time (PTT)**

PT and PTT will be expressed as an International Normalized Ratio (INR) or in seconds.

18. **Electrocardiogram (ECG)**

All ECGs must be 12-lead ECGs. An ECG is required at screening to determine eligibility – this may be a single ECG. Triplicate ECGs must be taken on Cycle 1, Day 1 before the first dose of AP26113. Triplicate ECGs must be taken on Cycle 2, Day 1 (Day 29) prior to administration of the Cycle 2, Day 1 dose, and at 1, 2, 4, and 6 hours after dosing of AP26113. Triplicate ECGs should be taken 1 to 2 minutes apart over a 5 minute timeframe. ECG measurements should coincide with the PK measurements that have the same time points. As such, triplicate ECGs should be taken directly before obtaining the PK sample at the allotted time points on Cycle 1, Day 1 and Cycle 2, Day 1. Subsequent ECGs (after Cycle 2, Day 1) only need to be done once.

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).

ECGs will be recorded electronically and will be evaluated centrally. For consistency, the Fridericia correction – QTcF – method must be used for all calculating of QTc intervals.

19. **Safety Assessments – Adverse Events**

Patients must be followed for all adverse events (AEs) from the date the informed consent is signed until at least 30 Days After the End of Treatment, and for all serious or study drug-related toxicities until the AEs are resolved or are considered chronic or stable or until patient contact discontinues. Serious adverse events (SAEs) should be monitored and reported as described in Section 7.

Type, incidence, severity (graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 4.0, see Attachment 1), timing, seriousness and relatedness, outcome, action taken with study drug, and treatment will be assessed and documented by the investigator throughout the study (see Section 7).

Malignancy-related signs and symptoms noted at study entry will be recorded as AEs during the trial if they worsen in severity or increase in frequency.

20. **Concomitant Medications**

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 the End of Treatment, 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.

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 at the End of Treatment.

22. **Disease Assessment**

At screening, disease assessment must include imaging of the chest, abdomen, pelvis and brain using appropriate radiological procedures (computed tomography [CT] scan, MRI scan) and physical examination (for palpable lesions). A contrast enhanced brain MRI (such as gadolinium) is required for all patients at baseline and for patients who have CNS metastases at follow-up visits. Target and non-target lesions must be selected at study start and followed throughout the course of treatment for response assessment according to RECIST guidelines (provided in Attachment 3). CNS lesions previously treated with SRS are not evaluable and should not be selected as either target or non-target lesions. All radiographic images (eg, CT scan, MRI) performed during the trial will be submitted to and stored by an imaging core lab for future independent evaluation as appropriate.

Disease assessment will be performed at screening, and at 8-week intervals through Cycle 15, and at 12-week intervals from Cycle 16 through End of Treatment, for all cohorts, and may be limited to sites of disease. The allowable window for the tumor imaging screening assessment is 21 days prior to Day 1. However, whenever feasible, baseline imaging should be performed as close as possible to Cycle 1, Day 1. Imaging assessment is also required to be performed at the End of Treatment.

Note: RECIST-defined responses will be confirmed with an imaging assessment at a 4-week interval. For patients in cohort 5, cMRI must reveal at least one measurable brain lesion (≥ 10 mm at the longest diameter) at screening as the target lesion. All imaging scans should include a slice thickness of 1 mm, ideally, and up to 5 mm as a maximum.

23. **Survival**

All patients should be followed-up for survival at least every 3 months, up to 2 years after the initial dose of AP26113.

24. **Tissue and Research Blood Samples**

Screening:

At entry, all patients must provide tumor tissue for analysis of genetic alterations, a blood sample as a normal comparator (approximately 3 mL), and a blood sample for analysis of circulating tumor DNA in plasma (approximately 20 mL). Both screening blood samples may be taken at the same time as the blood samples drawn for screening serum chemistry and hematology. If tumor tissue is not available, the patient must undergo a biopsy to obtain an adequate sample.

Patients entering the study into cohorts for whom failure of a prior TKI therapy is an eligibility requirement (expansion cohorts 2, 3, and 5) must have available tumor tissue taken after the time of progression on the most recent TKI treatment course.

Formalin-fixed, paraffin-embedded (FFPE) tumor tissue must be provided as a paraffin block or as slide sections. The minimum amount of tumor tissue required is 1 cubic mm, with at least 20% nucleated tumor cellularity. Patients with less tissue than required can be enrolled only with prior approval from the Sponsor.

Active Study Period:

All patients must provide a blood sample (approximately 20 mL) concomitant with each disease assessment (ie, at every 8 weeks through Cycle 15, and every 12 weeks from Cycle 16 through End of Treatment). Plasma derived from the blood samples will be used to quantitatively assess tumor mutations in circulating DNA.

Post-treatment:

An optional post-treatment biopsy at time of progression (for patients whose best response was not progressive disease) will be taken. As at screening, the minimum amount of FFPE tissue required is 1 cubic mm, with at least 20% nucleated tumor cellularity.

Post-progression tissue will be analyzed at Foundation Medicine to identify mutations that may inform treatment decisions following progression on AP26113. The results of these tests will be provided to the Investigator and the Sponsor immediately after analysis per the testing procedures.

25. **Cerebrospinal Fluid Sampling**

If lumbar puncture (LP) is performed as part of the standard of care, remaining CSF samples should be analyzed to determine the concentration of AP26113 (≥ 500 µL is sufficient), and these samples should have matched blood samples (for PK analyses) when possible.

26. **PK Sampling**

To determine AP26113 and AP26123 (a metabolite of AP26113) plasma levels, 3 mL of whole blood will be collected into an EDTA K2 tube (lavender top) as described below and in the Schedule of Events.

Dose Escalation Phase:

Cycle 1 PK: During Cycle 1, blood samples will be collected immediately prior to the first dose (time 0), and 0.5, 1, 2, 4 (± 10 minutes), 6, 8 (± 20 minutes), and 24 hours (± 60 minutes) after the first dose. The 24-hour sample will be collected prior to drug administration on Cycle1, Day 2. Blood samples will also be collected prior to dosing on Cycle 1, Days 8, 15, and 22.

Cycle 2 PK: During Cycle 2, samples will be collected before dosing and 0.5, 1, 2, 4 (± 10 minutes), 6, 8 (± 20 minutes), 24, and 48 hours (± 60 minutes) after administration of AP26113 on Cycle 2, Day 1. No drug will be administered on Cycle 2, Day 2. If multiple daily doses (eg, BID dosing) are employed, only the first dose on Cycle 2, Day 1 will be administered. The 48-hour sample will be collected before administration of the dose on Cycle 2, Day 3.

Cycle 3 PK: A single PK sample will also be collected pre-dose on Cycle 3, Day 1.

Expansion Phase PK:

PK evaluation will also be performed for the expansion cohorts to obtain cohort-specific single-dose and trough PK at the recommended dose established in the dose escalation phase of the trial. PK sampling time points will be the same as the sampling time points in

the dose escalation phase; however, adjustments may be made based on the PK findings in the dose escalation phase.

5.2 Screening Period

The screening period begins when the informed consent form is signed, and continues until the first dose of AP26113 is administered. Screening assessments should 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. Screening physical examination, vital signs, ECOG Performance Status assessments, hematology, chemistry, insulin, urinalysis and PT/PTT, and pregnancy test assessments can each also be used as the Day 1 assessment, without the need for having to repeat the tests, if these screening assessments are accomplished within 7 days prior to Day 1 AND, in the opinion of the investigator, there is no reason to believe they have substantially changed.

Assessments required at screening are shown on the Schedule of Events. A detailed description of procedures and timing is provided in Section 5.1. In addition, all patients must provide tumor tissue for analysis. If tumor tissue is not available, the patient must undergo a biopsy to obtain adequate samples.

5.3 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.

5.4 Active Study Period

The active study period begins when the patient receives the first dose of AP26113.

Assessments required during the active study period are shown on the Schedule of Events. A detailed description of procedures and timing is provided in Section 5.1. In summary, physical examination, vital signs, ECOG Performance Status, clinical laboratory assessments (hematology, chemistry, urinalysis, insulin, coagulation [PT/PTT]), and ECGs will be performed at Cycle 1 Day 1, Cycle 2 Day 1, every 28 days from Cycle 3 onwards (at Day 1 of each cycle), at End of Treatment, and at 30 Days After End of Treatment. Disease assessment will be performed at Cycle 1 Day 1, and at every 8 weeks through Cycle 15, then at every 12 weeks from Cycle 16 through End of Treatment. In addition, at Cycle 1, Day 15 additional clinical laboratory assessments are required (hematology, chemistry, insulin, and PT/PTT only).

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.

5.5 End of Treatment

The End of Treatment is defined as the point when the patient receives the last dose of AP26113 or the patient discontinues taking AP26113. Study procedures at the End of Treatment must be conducted within 14 days following the last dose of study drug.

Assessments required at the End of Treatment are shown on the Schedule of Events. A detailed description of procedures and timing is provided in Section 5.1.

5.6 30 Days after End of Treatment

A patient is required to complete all post treatment discontinuation assessments 30 Days After End of Treatment. Study procedures at 30 Days After End of Treatment must be conducted within 30 days (± 7 days) following the last dose of study drug.

Assessments required at 30 Days After End of Treatment are shown on the Schedule of Events. A detailed description of procedures and timing is provided in Section 5.1.

5.7 Follow-up Period

The follow-up period for a patient begins after the last completed assessment during the active study period and continues until patient contact ceases. All patients should be followed for survival at least every 3 months (± 14 days), up to 2 years after the initial dose of AP26113. For patients who discontinue the study treatment due to a reason other than progressive disease, additional tumor assessments should be documented, if available, until disease progression or start of another systemic anti-cancer therapy.

5.8 Study Duration

The expected total duration of patient participation is approximately 2 years, including a 2- to 3-week screening period, an estimated average of 10 to 12 cycles (28 days each) of AP26113 in responding patients (participation for patients who do not respond will most likely be of shorter duration), and the 30-day after treatment discontinuation assessments. In addition, patients should be followed-up for survival at least every 3 months, up to 2 years after the initial dose.

The total estimated duration of the study is 4 years, including 24 months to accrue patients with 2 years for treatment and follow-up for the last patient. Patients who are still on study at 2 years will be allowed to receive study drug beyond 2 years until disease progression or they discontinue treatment for other reasons.

5.9 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; In some cases, despite progression by RECIST, patients and investigators may have the opinion that continued study drug administration is beneficial, and in these cases, therapy may continue with the Sponsor's agreement.
- Entry into another therapeutic clinical trial or start of additional 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 and decision to discontinue participation;
- Termination of the trial 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 trial for any reason, every effort must be made to perform all End of Treatment and 30 Days After End of Treatment assessments per the schedule of events. 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 the active study period will be followed-up for survival for at least 3 months and up to 2 years after initial dose of AP26113. For patients who discontinue the study treatment due to a reason other than progressive disease, additional tumor assessments should be documented, if available, until disease progression or start of another systemic anti-cancer therapy.

5.10 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), and International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

5.11 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 and CSF samples must be stored at -20ºC until shipment. Specific instructions regarding the handling and shipment of these specimens will be provided in the Study Reference Manual.

6 STUDY TREATMENT(S)

6.1 Study Drug

AP26113 is a novel, synthetic, orally active TKI that potently inhibits activated, mutant forms of ALK and EGFR.

6.2 Selection of Starting Dose

The starting dose of AP26113 in the initial phase 1/2 clinical trial is 30 mg/day. This dose level was selected on the basis of data obtained from the 28-day oral toxicology studies in rats and monkeys (see Section 1.2.4 for more details on the rationale for starting dose selection).

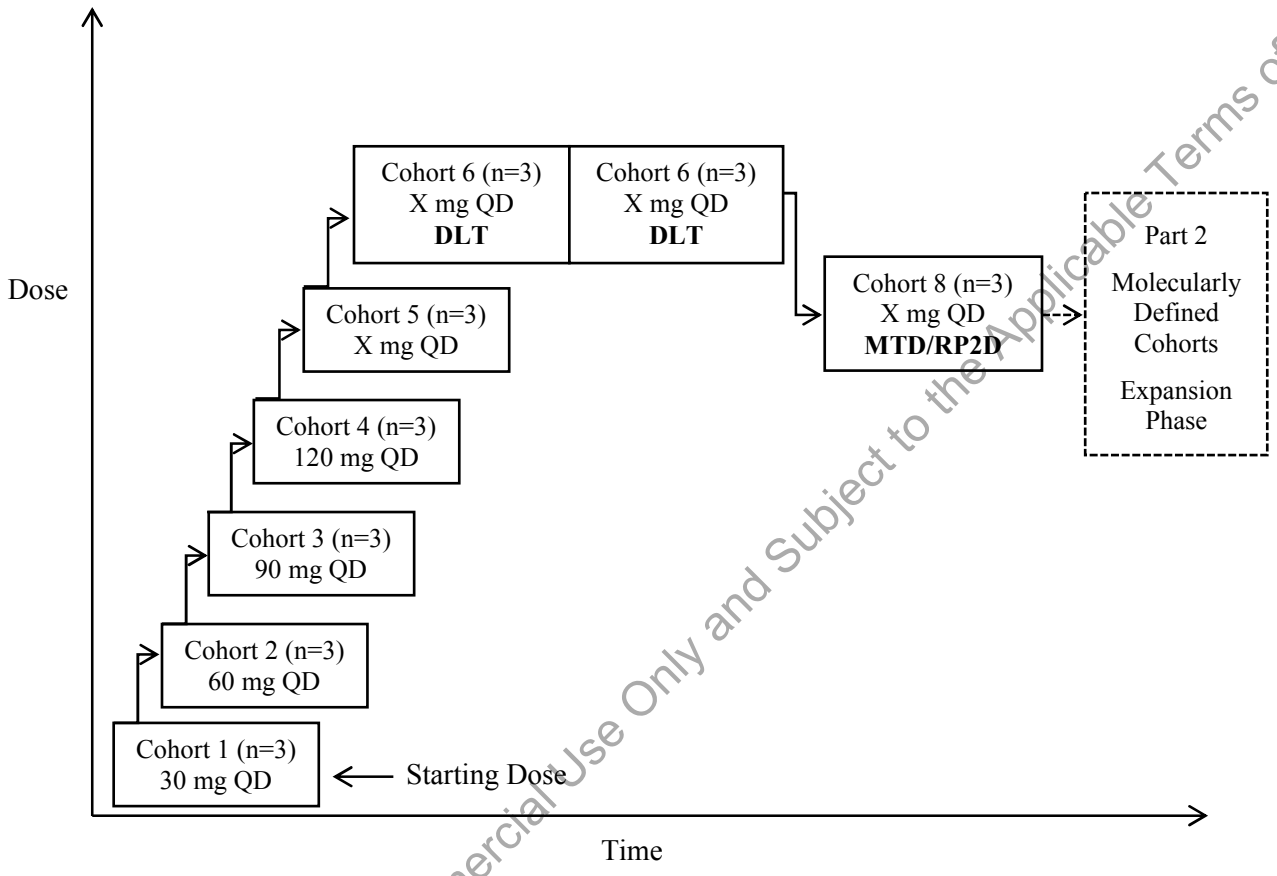
6.3 Treatment Administration

AP26113 will be administered orally in capsules or tablets, each consisting of 30 mg of AP26113 active pharmaceutical ingredient. Changes to the strength and composition of the tablets and capsules may be made during the course of AP26113 development. Study drug (AP26113) will be self-administered by the patient. The starting dose will be 30 mg taken orally once daily. Each 28-day dosing period is referred to as 1 cycle. Patients will take the prescribed dose with water approximately 2 hours after a light meal. Patients will be instructed not to eat or drink anything other than water for 2 hours after taking their dose. 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.

6.4 Dose Escalation

The dose escalation phase of this phase 1/2 trial will employ sequential dose escalation of oral AP26113 using a standard 3+3 design, starting at 30 mg administered orally once daily, and increasing in increments until the MTD is identified. Figure 2 provides a schematic representation of the dose escalation phase of the study. The following guidelines are provided; however, decisions for dose escalation will be made in conference with the Investigator and Sponsor. Doses in between or higher than those shown in the following guidance may be explored.

Figure 2 Schematic of AP26113 Phase 1/2 Trial Design – Dose Escalation Phase



Key: DLT=Dose Limiting Toxicities. MTD=Maximum Tolerated Dose. RP2D=Recommended Phase 2 Dose. QD=once daily.

Initially, 3 patients will be enrolled, will take 30 mg of AP26113 administered orally once daily, and will be followed for 28 days. The next scheduled dose is 60 mg, followed by the 90 and 120 mg dose level cohorts. Further dose escalation will involve increments of no more than 50% of the previous dose depending on safety findings. Multiple doses (eg, twice daily) may be administered daily based on PK findings (eg, $t_{1/2}$) for the initial patients.

The number of patients in each dose level cohort may vary depending on the events of the study, but cohorts will have a minimum of 3 patients enrolled. At each dose level, 3 patients will be enrolled initially and followed for 28 days. Increasing to the next dose level will depend on the safety findings of the previous cohort. If no DLTs are observed, the next higher cohort will begin enrollment. Expansion of a cohort from 3 to 6 patients will occur if 1 of 3 patients experiences a DLT at a given dose. If this occurs, 3 more patients will be enrolled at that dose level. If 1 or more patients exhibit a DLT, the dose level will be designated to have exceeded the MTD. If none experience a DLT, dose escalation will continue. Expansion of the cohort size may also occur at any dose to confirm safety observations.

Further dose escalation, multiple doses, and dose modifications may occur as described in Section 6.5.

The maximum administered dose in the trial will likely exceed the MTD. Intermediate doses between the MTD and the next lower dose may be explored. Schedules for single or multiple dosing of AP26113 in a given period may be explored depending on PK findings.

6.4.1 Intra-Patient Dose Escalation

Intra-patient dose escalation will be allowed according to the following scheme. All patients will have the option to increase dose while on study if the following conditions are met: 1) the patient tolerated his/her starting dose without a DLT and s/he remains on study without disease progression, 2) the Cycle 2 PK samples have been drawn per protocol, and 3) the proposed next dose level has been evaluated and it has been shown that it does not exceed the MTD.

6.4.2 Maximum Tolerated Dose (MTD)

The MTD is defined as the highest dose at which ≤ 1 of 6 evaluable patients experience a DLT within the first 28 days of treatment (end of Cycle 1). Evaluable patients must complete at least 75% of their planned doses, unless missed doses are due to related AEs. The cohort may be expanded to better define the safety profile or for confirmation of the MTD. The maximum administered dose in the trial will likely exceed the MTD.

6.4.3 Dose-Limiting Toxicities (DLTs)

DLTs will be summarized by category (hematologic and non-hematologic) and by Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term. Standard AEs will be considered DLTs that count for the determination of the MTD of AP26113. A DLT is a drug-related toxicity that is observed to occur within the first 28 days of treatment (end of cycle 1) as defined below. Drug-related toxicities include any toxicity that is possibly, probably, or definitely drug-related. Toxicity grades will be defined by the NCI CTCAE v 4.0. DLTs are defined by the following:

- Non-hematologic toxicities
  i. Any grade ≥ 3 non-hematologic toxicity, with the exception of self-limiting or medically controllable toxicities (eg, nausea, vomiting, fatigue, electrolyte disturbances, hypersensitivity reactions) lasting < 3 days, and excluding alopecia.
- Hematologic toxicities
  i. Febrile neutropenia not related to underlying disease (fever, > 101°F; ANC < 500)
  ii. Prolonged grade 4 neutropenia (> 7 days)
  iii. Neutropenic infection: ≥ grade 3 neutropenia with ≥ grade 3 infection
  iv. Thrombocytopenia ≥ grade 3 with bleeding or grade 4 lasting ≥ 7 days
- Missed ≥ 25% of planned doses of AP26113 over 28 days due to treatment-related AEs in the first cycle.

6.5 Dose Modification(s)

Dose delays or reductions will be implemented as indicated in Table 2 for patients who experience adverse drug reactions due to non-hematologic (excluding pneumonitis events) or hematologic toxicity. After dose reduction, patients should continue therapy at the reduced dose. Dose reductions may be implemented a second time if additional toxicity ensues. If study drug is held for more than 2 weeks, resumption of therapy must be discussed with the Sponsor. In general, re-escalation of doses will occur only in consultation with the Sponsor, as stipulated in Section 6.5.1 below. If Grade 3 or 4 toxicity requiring dose reduction occurs in the first dose cohort, reduce dose by 50%.

For patients with pneumonitis events, dose delays or reductions will be implemented as indicated in Table 2. If a patient has a pneumonitis event Grade 1 or 2, AP26113 dosing should be withheld until patient recovers to baseline status; dosing should then be resumed as outlined in below. If a patient has an event of pneumonitis event Grade 3 or 4, dosing of AP26113 should be permanently discontinued.

Table 2 Dose Modifications for Non-hematologic/Hematologic Toxicity or Pneumonitis Events

Toxicity Grade	Action
Non-Hematologic Toxicity (excluding Pneumonitis Events)	
Grade 1	Continue therapy at same dose level.
Grade 2	Continue therapy at same dose level. If symptoms are intolerable, recurrent or not controlled by supportive care, withhold therapy until symptoms remit and reduce to next lower dose level.
Grade 3	Withhold therapy until toxicity is grade ≤ 1or has returned to baseline, then resume therapy. Therapy may be resumed at the same dose, or at the next lower dose level, based on the investigator's judgment.
Grade 4	Withhold therapy until toxicity is grade ≤ 1or has returned to baseline, then resume therapy at the next lower dose level. Therapy may also be discontinued based on the investigator's judgment.
Hematologic Toxicity	
Grade 1	Continue therapy at same dose level.
Grade 2	Continue therapy at same dose level.
Grade 3	Withhold therapy until toxicity is grade ≤ 2 or has returned to baseline, then resume therapy. Therapy may be resumed at the same dose, or at the next lower dose level, based on the investigator's judgment.
Grade 4	Withhold therapy until toxicity is grade ≤ 2 or has returned to baseline, then resume therapy at the next lower dose level. Therapy may also be discontinued based on the investigator's judgment.
Pneumonitis Events	
Grade 1	Withhold the dose until recovery to baseline, then resume at the same dose. If pneumonitis recurs, permanently discontinue treatment.
Grade 2	Withhold the dose until recovery to baseline, then resume at the next lower dose level (eg, 240 mg QD to 180 mg QD, 180 mg QD to 120 mg QD, 120 mg QD to 90 mg QD, or 90 mg QD to 60 mg QD). If pneumonitis recurs, permanently discontinue treatment.
Grade 3 or 4	Permanently discontinue treatment

6.5.1 Dose Re-escalation

Dosing reduced for toxicity may be re-escalated to the original dose only after discussion with the Sponsor. For dose re-escalation, the escalation dose must not exceed the MTD, and the patient must have recovered from the adverse event. For patients who continue the treatment despite radiologic disease progression (see Section 5.9), the dose may be escalated to a higher dose that is determined not to exceed the MTD, following discussion with the Sponsor.

6.6 Initiation of Expansion Phase Enrollment

The decision to proceed from the dose-escalation portion of the study and to open the expansion cohorts will depend on establishing that AP26113 can be administered safely. Enrollment in expansion cohorts will be dependent on observing evidence of disease response in the dose escalation cohort. Once the RP2D is identified, patients will be enrolled into the molecularly defined expansion cohorts comprising Part 2 of the study design (Figure 1). The expansion phase will include 5 additional histologically and molecularly defined cohorts, with cohort 5 being limited to patients with active brain metastases (Figure 1). The dose and schedule for the expansion cohorts will be determined based on the RP2D and schedule determined in the dose escalation phase of the trial. Additional dosing strategies may be evaluated in the expansion cohorts to gather additional safety and efficacy data at a dose below the current RP2D.

6.7 Prior and Concomitant Medications

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 course of the trial for underlying medical conditions and management of symptoms. Patients with CNS lesions requiring SRS are allowed to continue the study treatment after appropriate interruption; however, for analysis purposes, these patients will be considered to have progressive disease.

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 the End of Treatment, 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.

6.8 Prohibited Treatment(s)/Therapy

The following concurrent medications 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 Attachment 4). Medications that prolong the QT interval, but are not known to be associated with Torsades, should be avoided, but are not prohibited;
4. Herbal preparations or related over-the-counter preparations containing herbal ingredients;
5. Extensive surgery requiring in-patient care (patients may have an interruption in therapy for 14 days should emergency surgery be required).

Medications that are potent inhibitors or inducers of P450 cytochromes, in particular CYP2C8 and CYP3A4, should be avoided.

Patients should avoid using AP26113 in combination with other agents known to cause bradycardia (eg, beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin). The investigator or qualified designee should also educate patients not to start on any over-the-counter (OTC) medications, herbal or prescription medications that may affect heart rate, and to consult with the investigator prior initiating any therapy.

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.

6.9 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.

6.10 Treatment(s) Supply

Upon receipt of clinical trial 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.

6.10.1 Formulation, Packaging, and Labeling

AP26113 drug product is supplied as either capsules or tablets, containing 30 mg of AP26113 active pharmaceutical ingredient. Any excipients used to manufacture the drug product will be of pharmaceutical grade. The drug product is manufactured under Current Good Manufacturing Practice (CGMP) during the course of the trial. AP26113 will be supplied in white high density polyethylene (HDPE) bottles with child-resistant caps with liner.

Bottle 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 capsules or tablets, and lot number.

6.10.2 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 approved by the Sponsor. 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.

6.10.3 Treatment(s) Storage and Accountability

The recommended storage condition for AP26113 is controlled room temperature.

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 of study drug must be 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 trial 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 trial, 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.

7 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Event

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.

AEs include:

- Abnormal test findings
- Changes in physical examination findings
- Other untoward medical events, regardless of their relationship to the study drug, such as injury, events that require surgery, accidents, or apparently unrelated illnesses
- Hypersensitivity

Additionally, AEs may include signs or symptoms resulting from:

- Drug overdose
- Drug withdrawal
- Drug abuse
- Drug misuse
- Drug interactions
- Drug dependency
- Exposure in utero

7.1.2 Serious Adverse Event

The Investigator or Sponsor will determine the seriousness of an AE based on the following:

An AE is considered a SAE if at least one (1) 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* is defined as 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 trial is considered a SAE. A new cancer is a cancer that is histopathologically different than the cancer under study in the trial (ie, does not include metastatic or progressive disease).
- *Overdose*: Any AE associated with an overdose of study drug. An overdose of study drug is defined as an occurrence of administered dose exceeding that which is prescribed by the investigator per protocol.
- *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.

7.1.2.1 Progression of the malignancy under study (including signs and symptoms of progression)

Worsening of signs and symptoms of the malignancy under trial 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 unless the progression requires inpatient hospitalization or results in death. In that case, the event should be reported as an SAE.

7.1.2.2 Hospitalizations

AEs reported from clinical trials 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
- 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 a SAE. Examples include:

- Social admission (eg, patient has no place to sleep)

- Protocol-specified admission during a clinical trial (eg, for a procedure required by the trial 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.

7.1.3 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 trial, significant additional concomitant drug treatment, or other therapy.
- Test result is considered to be an AE by the investigator or sponsor.

7.1.4 Expectedness

The expectedness of a SAE is assessed by the Sponsor in the overall classification of SAEs for regulatory reportability. The current Investigator's Brochure section "Summary of Data and Guidance for the Investigator" will be used as the reference for determination of expectedness and risk assessment.

7.2 Evaluation of Adverse Events and Serious Adverse Events

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 criteria for classification as a SAE (see Section 7.1.2) requiring immediate notification to ARIAD or its designated representative.

The investigator will document the following assessments for all adverse events and serious adverse events in accordance with applicable guidelines for completion of the eCRF and the Serious Adverse Event Report form.

7.2.1 Adverse Event Severity

The severity of AEs will be assessed according to the NCI CTCAE, Version 4.0. 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. The AE does not require discontinuing administration or reducing the dose of the study drug.

- *Moderate (Grade 2)*: The AE interferes with routine activity, but responds to symptomatic therapy or rest. The AE may require reducing the dose, but not discontinuing administration of the study drug.
- *Severe (Grade 3)*: The AE significantly limits the patient's ability to perform routine activities despite symptomatic therapy. In addition, the AE leads to discontinuing administration or reducing the dose of the study drug.
- *Life Threatening (Grade 4)*: The AE requires discontinuing administration of the study drug. 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 administration of the study drug.

7.2.2 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 a SAE is associated with trial 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 study 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 study 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 (study 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 (study 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 (study 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.

7.3 Serious Adverse Event Reporting Procedures

7.3.1 Serious Adverse Event Reporting Period

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

Once a patient is deemed a screen failure, AE collection is no longer required (see Section 5.3 Screen Failures).

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

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

7.3.2 Reporting Serious Adverse Events

The investigator or investigator's designee must notify ARIAD Pharmacovigilance and Risk Management or its designated representative immediately (within 24 hours) after becoming aware of an SAE. This timeframe also applies to additional new information (follow-up) on previously reported SAEs.

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

Information should be provided on the Serious Adverse Event Report form signed and dated by the Investigator. 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

7.3.4 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 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.

7.3.5 Required Follow-up for Serious Adverse Events

There should be routine follow-up for 30 days after permanent discontinuation of study drug in all patients in order to monitor for the occurrence of SAEs. If an SAE continues after the 30-day evaluation period, then the patient must be followed until the event resolves or stabilizes. The medical monitor may specify a longer period of time, if required to assure the safety of the patient.

7.4 Sponsor Responsibility for Expedited Safety Reports

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

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

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

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

7.5 Other Safety Issues

7.5.1 Pregnancy

Females of childbearing potential and fertile males will be informed as to the potential risk of conception while participating in this study and will be advised that they must use effective contraception during the dosing period and for a period of at least 30 days thereafter for females and 120 days for males. A pregnancy test will be performed on each pre-menopausal female of childbearing potential immediately prior to the first dose of study drug, 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 trial, 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.

8 PLANNED STATISTICAL METHODS

8.1 General Considerations

The dose escalation phase of this phase 1/2 trial will employ sequential dose escalation of oral AP26113 using a standard 3+3 design, starting at 30 mg administered orally once daily, and increasing in increments until the MTD is identified.

Descriptive statistics and analyses will be provided for each dose level, and for patients combined across dose levels where applicable.

Data from patients in the expansion phase cohorts will be summarized together with data from patients in the dose escalation cohorts, as appropriate. 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, treatment administration/compliance, efficacy, safety, and pharmacokinetic parameters. Data will also be displayed graphically, where appropriate.

8.1.1 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;
- 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.

8.2 Study Endpoint(s)

8.2.1 Primary Endpoint(s)

The primary endpoint of the dose escalation component of the study is the RP2D of orally administered AP26113. The primary endpoint of expansion cohorts 1-4 is the overall response rate (using RECIST). The primary endpoint of expansion cohort 5 is CNS response rate (using RECIST).

8.2.2 Secondary Endpoint(s)

Secondary endpoints of the dose escalation component of the study include:

1. MTD of orally administered AP26113
2. Safety, tolerability, and DLTs of AP26113
3. Plasma PK parameters of single-dose and steady state AP26113

Secondary endpoints of the expansion cohort component of the study include:

1. Safety and tolerability of AP26113
2. Plasma PK parameters

3. Efficacy assessments include: best target lesion response, PFS, TTP, and time to treatment failure in patients who remain on study after RECIST progression, but who continue to benefit according to the treating investigator. Overall survival (OS) will also be measured for up to 2 years following the first dose of AP26113.

   - For cohort 5: additional efficacy assessments include: overall response rate using RECIST, CNS PFS, and extra CNS PFS.

8.2.3 Other Endpoints

CCI

[redacted]

8.3 Determination of Sample Size

The purpose of this phase 1/2 trial is to determine the RP2D, MTD, safety, tolerability and preliminary efficacy of oral AP26113 in patients with advanced malignancies other than leukemia. The sample size is determined based on clinical rather than statistical considerations. The number of patients in this trial is consistent with phase 1 dose finding studies; the histologically and molecularly defined expansion cohorts will facilitate obtaining preliminary estimates of clinical activity. With this design, the estimate of the rate of DLT at the MTD is in the range of 0.17 to 0.26. The estimate of the rate of DLT at the highest dose, which is 1 step above the MTD, is 0.33 (Ting, 2006).

8.4 Definition of Analysis Populations

All patients who receive at least 1 dose of AP26113 will be included in the analyses.

8.5 Efficacy Analysis

For the expansion cohorts, preliminary estimates of clinical activity including response rate, PFS, TTP and best target lesion response will be determined. When appropriate, data from patients in the expansion cohorts will be summarized together with data from patients in the dose escalation phase.

For each cohort and tumor type, the best response (complete response [CR], partial response [PR], stable disease [SD] or progressive disease [PD] according to RECIST – see Attachment 3) for each patient with measurable disease who received at least one (1) dose of study medication will be listed. Time to response will be evaluated using the Kaplan-Meier method treating progression as a competing risk. Response at 6 and 12 months will be computed using the

Kaplan-Meier estimate. The PFS, TTP and OS will be analyzed using the Kaplan-Meier method. Median time to progression and progression rates at 6 months and 12 months will be computed along with CIs. The OS rates at 12 and 24 months and associated CIs will be computed. Best target lesion response will be displayed using a "waterfall" plot.

Patients' molecular genetic status will be characterized by both mutation history and central testing results obtained from the tumor tissue sample provided at study entry in order to explore molecular genetic features that are associated with the anti-tumor activity of AP26113. Data obtained from the central laboratory will be used to support the development of a well-validated test that can be used in future studies to prospectively identify patients with tumors with such features.

8.6 Safety Analysis

Safety assessments will include physical and laboratory examinations, vital signs, and ECGs. Adverse events will be graded according to the NCI CTCAE v 4.0. Periodic meetings with study investigators will be held to assess safety throughout the trial.

All patients receiving at least 1 dose of AP26113 will be considered evaluable for safety. The 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.

8.6.1 Pharmacokinetic Analysis

Parameters: maximum concentration (C_{max}), time of maximum concentration (T_{max}), area under the curve (AUC; over the first 24 hours), and drug elimination half-life ($t_{1/2}$), will be estimated from plasma concentration data using non-compartmental methods. The geometric mean and 95% CIs will be reported. Accumulation for C_{max}, and AUC will be estimated from plasma concentration levels on Cycle 1, Day 1 (Day 1) and Cycle 2, Day 1 (Day 29), using the geometric mean ratio and 95% CI. Dose linearity for C_{max} and AUC will be assessed using regression methods.

8.6.2 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. The Fridericia correction (QTcF) will be used throughout. QTcF change from baseline and blood concentration will be analyzed using mixed effects models.

8.7 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 study closure and will be listed by dosing cohort in the clinical study report.

9 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.

9.1 Investigators and Study Administrative Structure

The Investigator must provide the Sponsor with the following documents BEFORE enrolling any patients:

- An executed Clinical Trial Agreement,
- FDA Form 1572,
- Documentation of financial disclosure,
- Principal Investigator's Curriculum Vitae,
- IRB/EC approval of the protocol,
- IRB/EC approved 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 will accept 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 and the FDA for any changes in the study personnel reported in the current FDA Form 1572.

9.2 Study Monitoring

This study will be monitored by a representative 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).

10 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 Good Clinical Practice (GCP) guidelines and the applicable regulatory requirements.

10.1 Institutional Review Board (IRB) or Ethics Committee (EC) Approval

The protocol and the informed consent document must have the initial and at least 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 also should 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.

10.2 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 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.

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.

10.3 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.

11 DATA HANDLING AND RECORD KEEPING

11.1 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 trial. All pertinent data records are to be submitted to the Sponsor during and/or at completion or termination of the study.

11.2 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.*

11.3 Retention of Data

Trial 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). Trial 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.

12 PUBLICATION AND DISCLOSURE POLICY

The Investigator must notify the IRB/EC of the conclusion of the clinical trial. 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 trials 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 trial registration as a condition for publication of research results generated by a clinical trial. (http://www.icmje.org [Accessed: 18 December 2013]).

The Institution and Principal Investigator acknowledge that the study is a 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 forty-five (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 the Institution and/or Principal Investigator publishes the results of the Study, the Institution and/or Principal Investigator hereby grant(s) 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.

13 REFERENCES

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ATTACHMENT 1 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, v.4.0) can be found on the following website.

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40 [Accessed: 18 December 2013]

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.

ATTACHMENT 2 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, Horton J, Davis TE, McFadden ET, Carbone PP. 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.

ATTACHMENT 3 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST VERSION 1.1)

Eisenhauer, E. A., Therasse P., Bogaerts J., Schwartz L. H., Sargent D., Ford R., Dancey J., Arbuck S., Gwyther S., Mooney M., Rubinstein L., Shankar L., Dodd L., Kaplan R., Lacombe D., & Verweij J. (2009). New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *European Journal of Cancer*, *45*, 228-247.

ATTACHMENT 4 DRUGS WITH A RISK OF TORSADES DE POINTES

The website http://www.crediblemeds.org/everyone/composite-list-all-qtdrugs/ [Accessed: 15 February 2017] 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 4.1 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
Anagrelide	Agrylin, Xagrid	Phosphodiesterase 3 inhibitor / Thrombocythemia
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
Cilostazol	Pletal	Phosphodiesterase 3 inhibitor / Intermittent claudication
Ciprofloxacin	Cipro, Cipro-XR, Neofloxin	Antibiotic / Bacterial infection
Cisapride	Propulsid®	GI stimulant / heartburn

Generic Name	Brand Name	Class/Clinical Use
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
Donepezil	Aricept	Cholinesterase inhibitor / Dementia (Alzheimer's Disease)
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

Generic Name	Brand Name	Class/Clinical Use
Flecainide	Tambocor®, Almarytm®, Apocard®, Ecrinal®, Flécaine®	Antiarrhythmic / abnormal heart rhythm
Fluconazole	Diflucan, Trican	Antifungal / Fungal infection
Gatifloxacin (Removed from Market)	Tequin	Antibiotic / Bacterial infection
Grepafloxacin (Removed from Market)	Raxar	Antibiotic / Bacterial infection
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
Ibogaine (Only on Non US Market)	None	Psychedelic / Narcotic addiction, unproven
Ibutilide	Corvert®	Antiarrhythmic / abnormal heart rhythm
Levofloxacin	Levaquin, Tavanic	Antibiotic / Bacterial infection
Levomepromazine (Only on Non US Market)	Nosinan, Nozinan, Levoprome	Antipsychotic / Schizophrenia
Levomethadyl	Orlaam®	Opiate agonist / pain control, narcotic dependence
Levosulpiride (Only on Non US Market)	Lesuride, Levazeo, Enliva (with rabeprazole)	Antipsychotic / Schizophrenia
Mesoridazine	Serentil®	Antipsychotic / schizophrenia

Generic Name	Brand Name	Class/Clinical Use
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
Oxaliplatin	Eloxatin	Antineoplastic Agent / cancer
Papaverine HCl (Intra-coronary)	none	Vasodilator, Coronary / Diagnostic adjunct
Pentamidine	Pentam®, NebuPent®	Anti-infective / pneumocystis pneumonia
Pimozide	Orap®	Antipsychotic / Tourette's tics
Probucol	Lorelco®	Antilipemic / Hypercholesterolemia
Procainamide	Pronestyl®, Procan®	Antiarrhythmic / abnormal heart rhythm
Propofol	Diprivan, Propoven	Anesthetic, general / Anesthesia
Quinidine	Quinaglute®, Duraquin®, Quinact®, Quinidex®, Cin-Quin®, Quinora®	Antiarrhythmic / abnormal heart rhythm
Roxithromycin (Only on Non US Market)	Rulide, Xthrocin, Roxl-150, Roxo, Surlid, Rulide, Biaxsig, Roxar, Roximycinv, Roxomycin, Rulid, Tirabicin, Coroxin	Antibiotic / Bacterial
Sevoflurane	Ulane®, Sojourn®	Anesthetic, general / anesthesia
Sotalol	Betapace®, Sotalex®, Sotacor®	Antiarrhythmic / abnormal heart rhythm

Generic Name	Brand Name	Class/Clinical Use
Sparfloxacin	Zagam®	Antibiotic / bacterial infection
Sulpiride (Only on Non US Market)	Dogmatil, Dolmatil, Eglonyl, Espiride, Modal, Sulpor	Antipsychotic, atypical / Schizophrenia
Sultopride (Only on Non US Market)	Barnetil, Barnotil, Topral	Antipsychotic, atypical / Schizophrenia
Terfenadine (Removed from Market)	Seldane®	Antihistamine / allergic rhinitis
Terlipressin (Only on Non US Market)	Teripress, Glypressin, Terlipin, Remestyp, Tresil, Teriss and others	Vasoconstrictor / Septic shock
Terodiline (Only on Non US Market)	Micturin, Mictrol (not bethanechol)	Muscle relaxant / Bladder
Thioridazine	Mellaril®, Novoridazine®, Thioril®	Antipsychotic / schizophrenia
Vandetanib	Caprelsa®	Anticancer / thyroid cancer

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Clinical VP Approval	22-Mar-2017 07:22 GMT-04