Title: A Phase 2/3 Open-label Study to Evaluate Safety and Efficacy of Ponatinib, Followed by a Randomized Study of Ponatinib Versus Nilotinib in Patients with Chronic Myeloid Leukemia in Chronic Phase (CP-CML) Resistant to Imatinib

NCT Number: NCT02627677

Protocol Approve Date: 10 March 2017

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

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- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
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CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2/3 Open-label Study to Evaluate Safety and Efficacy of Ponatinib, Followed by a Randomized Study of Ponatinib Versus Nilotinib in Patients with Chronic Myeloid Leukemia in Chronic Phase (CP-CML) Resistant to Imatinib
Protocol Number:	AP24534-15-303
Study Phase:	2/3
Product Name:	Ponatinib
ClinicalTrials.gov Identifier:	NCT02627677
EudraCT Number:	2015-001318-92
Sponsor:	ARIAD Pharmaceuticals, Inc. 125 Binney Street Cambridge, MA 02142 USA Telephone: +1 (617) 494-0400
Protocol Issue Date:	10 March 2017
Version Number:	3.0

PROTOCOL REVISION HISTORY:

Amendment Number	Protocol Version Number	Date
Original Protocol	Version 1.0	29 April 2015
Amendment 1 (Canada only)	Version 1.1	08 September 2015
Amendment 2	Version 2.0	30 March 2016
Amendment 3	Version 3.0	10 March 2017

1 DISCLOSURE STATEMENT

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2 SIGNATURE PAGES

2.1 Signatory*

PPD

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

2.2 Investigator Signature

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

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

_____ _____

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

_____

Investigator's Name (print)

2.3 Sponsor Representative Signature

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

Sponsor Representative's Signature Date (dd-mmm-yyyy)

Sponsor Representative's Name and Title (print)

Clinical Research & Development

ARIAD Pharmaceuticals, Inc.

3 CONTACT INFORMATION

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Sponsor Medical Monitor:	PPD
Sponsor Additional Contact:	PPD

4 PROTOCOL SYNOPSIS

Sponsor	ARIAD Pharmaceuticals, Inc. 125 Binney Street Cambridge, MA 02142 USA
Study Treatment	Investigational medicinal product: Ponatinib Active comparator: None (phase 2); Nilotinib (phase 3)
Study Title	A Phase 2/3 Open-label Study to Evaluate Safety and Efficacy of Ponatinib, Followed by a Randomized Study of Ponatinib versus Nilotinib in Patients with Chronic Myeloid Leukemia in Chronic Phase (CP-CML) Resistant to Imatinib
Development Phase	Phase 2/3
Eligible Population	Patients with chronic phase chronic myeloid leukemia (CP-CML) who are resistant following first-line treatment with imatinib and have not received other tyrosine kinase inhibitors (TKIs)
Summary and Study Rationale	Most patients with newly diagnosed CML are initially treated with an imatinib regimen with good results (Henk et al, 2015). However, 30% to 50% of all newly diagnosed CP-CML patients who are treated in the first-line setting with imatinib are in need of another treatment, either because they become resistant to imatinib (20%-25%) or because they become intolerant of imatinib (15%-20%) (Baccarani et al, 2009). A review of efficacy in the second-line setting demonstrates that there is potential for improvement. Among the available second-line therapies (nilotinib, dasatinib, or bosutinib), major cytogenetic response (MCyR) rates in second-line CP-CML range from 51% with nilotinib therapy (n=321) (Nilotinib SmPC, 2016) to 62% in dasatinib treated patients (n=387) indicating that second-line therapy initially fails to achieve a response in a substantial fraction of patients. Additionally, none of the available second-line agents have activity against all of the known mutants and the T315I mutation is refractory to all TKIs with the exception of ponatinib. Thus, both with regard to response rates and activity against resistant mutants, an unmet need remains in many patients who fail first-line TKI therapy. Ponatinib is a novel, synthetic, orally active TKI specifically designed to optimally inhibit native BCR-ABL. It is also active against mutated forms of the protein that can arise during treatment with other TKIs and cause resistance, including the T315I gatekeeper mutant. This protocol describes a phase 2/3, open-label study of ponatinib for the treatment of patients with chronic myeloid leukemia (CML) in chronic phase (CP) whose imatinib therapy has failed. The goal of the phase 2 portion of this study is to generate efficacy and safety data to inform the design and sample size of the randomized phase 3 portion of this study. The goal of the phase 3 portion of this study is to test the hypothesis that ponatinib will be efficacious and safe in treating second-line CP-CML patients, that it will be superior to nilotinib, that each of the starting doses will demonstrate the continued efficacy of ponatinib, and that the dose reduction strategy will lessen arterial occlusive complications.

Study Design	This is a multi-center study to demonstrate the efficacy and safety of 1 dose of ponatinib during the phase 2 portion, and 2 starting doses of ponatinib as compared to nilotinib during the phase 3 portion. Eligible patients must have CP-CML, be resistant to first-line imatinib treatment and have received no other TKIs. During the phase 2 portion, all patients will receive ponatinib 15 mg once daily (QD). Upon achievement of major molecular response (MMR) as defined in the protocol, patients will have their daily dose of ponatinib reduced to 10 mg. Based on accumulating data from the 15 mg cohort in phase 2, the phase 3 design (including number of ponatinib cohorts) and/or sample size may be amended prior to enrollment of patients into the phase 3 portion of the study. During the phase 3 portion, patients will be randomized to receive once daily oral administration of either 30 mg ponatinib QD (Cohort A), 15 mg ponatinib QD (Cohort B), or 400 mg nilotinib BID (twice daily) (Cohort C). They will be randomized in a ratio of 1:2:1, respectively. Upon achievement of MMR as defined in the protocol, patients in Cohort A will have their daily dose of ponatinib reduced to 15 mg and patients in cohort B will have their daily dose of ponatinib reduced to 10 mg. The dose of nilotinib for patients in Cohort C will not be adjusted based on response. Ponatinib dose reduction upon achievement of MMR can also be implemented when an unscheduled response assessment is performed. The primary endpoint of MMR by12 months is defined according to standard criteria as ≤0.1% BCR-ABL1/ABL1^{IS}. The study will assess hematologic response, cytogenetic response, and molecular response, as well as additional measures of efficacy including time to responses, and duration of responses by starting dose and after dose reduction. Assessments will be according to standard international criteria. Progression-free survival (PFS) and overall survival (OS) data will also be collected and analyzed. Adverse event (AE) rates and rates of arterial occlusive events (AOEs) and venous thrombotic/embolic events (VTEs), in particular, will be measured. The duration of patient participation will be 60 months for all patients, unless they withdraw prior to that based on the withdrawal criteria defined within the protocol.

Study Objectives	**Primary Objective** **Phase 2** To demonstrate the efficacy of ponatinib administered at a dose of 15 mg QD in patients with CP-CML who are resistant to imatinib, as measured by MMR by 12 months **Phase 3** To demonstrate the efficacy of ponatinib administered at 2 starting doses (30 and 15 mg QD) compared to nilotinib administered at 400 mg BID in patients with CP-CML who are resistant to imatinib, as measured by MMR by 12 months **Key Secondary Objectives in Phase 2 and Each Cohort in Phase 3** • To characterize, according to each arm and ponatinib starting dose, the rate of AOEs and VTEs, AEs, and serious adverse events (SAEs) • To characterize, according to each arm and ponatinib starting dose, the rate of cytogenetic responses and molecular responses other than MMR • To further characterize efficacy according to each arm and ponatinib starting dose, including time to response, duration of cytogenetic and molecular response, duration of therapy, progression free survival, overall survival, and impact of dose escalation after loss of response (ponatinib cohorts only) **Other Secondary Objectives in Phase 2 and Each Cohort in Phase 3** • To characterize, according to each arm and ponatinib starting dose, the rate of discontinuation, dose reductions, and interruptions • To characterize, according to each arm and ponatinib starting dose, the rate of hematologic responses CCI [redacted]

Study Endpoints	**Primary Endpoint in Phase 2 and Each Cohort in Phase 3**
	Major molecular response (MMR) by 12 months for each cohort
	Key Secondary Endpoints in Phase 2 and Each Cohort in Phase 3
	• Cytogenetic response rates:
	  ○ Major cytogenetic response (MCyR) by 12 months
	  ○ Complete cytogenetic response (CCyR) by 12 months
	• Molecular response rates: ≤ 1% BCR-ABL1^{IS}, MR3/MMR, MR4, MR4.5 at 3-month intervals and MR1 (≤10% BCR-ABL1^{IS}) at 3 months
	• Safety
	  ○ Arterial occlusive and venous thrombotic/embolic events in each cohort
	  ○ AEs in each cohort
	  ○ SAEs in each cohort
	• Time to response
	• Duration of response:
	  ○ ≤ 1% BCR-ABL1^{IS} and MMR at 3, 6, 9, and 12 months, and then at 3-month intervals until completion of treatment
	  ○ MCyR at 12 months, by cytogenetic analysis
	  ○ Duration of response in responders
	  ○ Duration of therapy
	• Progression-free survival

	• Overall survival **Other Secondary Endpoints in Phase 2 and Each Cohort in Phase 3** • Hematologic response: complete hematologic response (CHR) • Tolerability: o Discontinuations due to AEs in each cohort o Dose reductions due to toxicity (prior to response) in each cohort o Dose interruptions in each cohort • Progression to accelerated phase (AP) or blast phase (BP) CML CCI [redacted]
Diagnosis and Main Inclusion Criteria	Patients must meet all of the following criteria to be eligible for the study: 1. Have CP-CML and are resistant to first-line imatinib treatment. a. The diagnosis of CML will be made using standard hematopathologic and cytogenetic criteria. CP-CML will be defined by all of the following: i <15% blasts in bone marrow ii <30% blasts plus promyelocytes in bone marrow iii <20% basophils in peripheral blood iv ≥100 × 10^9/L platelets (≥100,000/mm^3) v No evidence of extramedullary disease except hepatosplenomegaly vi No prior diagnosis of AP- or BP-CML b. Cytogenetic assessment must demonstrate the BCR-ABL1 fusion by presence of the t(9;22) Philadelphia chromosome. i Conventional chromosome banding must be performed ii A minimum of 20 metaphases must be assessable at entry. If < 20 metaphases are assessable, a real time PCR with > 1% of BCR-ABL1^{IS} is required to be eligible iii Variant translocations are not allowed c. BCR-ABL1 transcript levels must be assessable using the International Scale. (ie, patients must have either the b2a2 or b3a2 transcript type) d. Resistance is defined as follows. Patients must meet at least 1 criterion. i Three months after the initiation of therapy: No cytogenetic response (>95% Ph+) or failure to achieve CHR. ii Six months after the initiation of therapy: BCR-ABL1^{IS} >10% and/or >35% Ph+. iii Twelve months after the initiation of therapy: BCR-ABL1^{IS} >1% and/or Ph+ >0. iv At any time after the initiation of therapy, the development of new BCR-ABL1 kinase domain mutation(s). v At any time after the initiation of therapy, the development of new clonal evolution.

	vi At any time after the initiation of therapy, the loss of CHR, the loss of CCyR, or the confirmed loss of MMR in 2 consecutive tests, one of which has a BCR-ABL1^{IS} transcript level of ≥1%. [NOTE: The above criteria were adapted from Baccarani et al, 2013.] 2. Age ≥18 years old. 3. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. 4. Have adequate renal function as defined by the following criterion: a. Serum creatinine ≤1.5 × upper limit of normal (ULN) for institution. 5. Have adequate hepatic function as defined by all of the following criteria: a. Total serum bilirubin ≤1.5 × ULN, unless due to Gilbert's syndrome. b. Alanine aminotransferase (ALT) ≤2.5 × ULN or ≤5 × ULN if leukemic infiltration of the liver is present. c. Aspartate aminotransferase (AST) ≤2.5 × ULN or ≤5 × ULN if leukemic infiltration of the liver is present. 6. Have normal pancreatic status as defined by the following criterion: a. Serum lipase and amylase ≤1.5 × ULN. 7. Have a negative pregnancy test documented prior to enrollment (for females of childbearing potential). 8. Agree to use a highly effective form of contraception with sexual partners from the time of randomization through at least four (4) months after end of study treatment (for female and male patients who are fertile). 9. Provide written informed consent. 10. Be willing and able to comply with scheduled visits and study procedures. 11. Have recovered from toxicities related to prior anticancer therapy to NCI CTCAE grade ≤1 except for alopecia or peripheral neuropathy.
Main Exclusion Criteria	Patients are not eligible for participation in the study if they meet any of the following exclusion criteria: 1. Have previously been treated with any approved or investigational TKIs other than imatinib or treated with imatinib within 14 days prior to receiving study drug. 2. Have previously been treated with any anti-CML therapy other than hydroxyurea, including interferon, cytarabine, immunotherapy, or any cytotoxic chemotherapy, radiotherapy, or investigational therapy. 3. Underwent autologous or allogeneic stem cell transplant. 4. Are in ≤ 1% BCR-ABL1 (in phase 2) or in MMR (in phase 3). 5. Have a known history of T315I mutation in phase 3. 6. Have clinically significant, uncontrolled, or active cardiovascular disease, specifically including, but not restricted to: a. Any history of myocardial infarction (MI), unstable angina, cerebrovascular accident, or transient ischemic attack (TIA) b. Any history of peripheral vascular infarction, including visceral

infarction

c. Any history of a revascularization procedure, including vascular surgery or the placement of a stent

d. History of venous thromboembolism, including deep venous thrombosis, superficial venous thrombosis, or pulmonary embolism, within 6 months prior to enrollment

e. Congestive heart failure (New York Heart Association [NYHA] class III or IV) within 6 months prior to enrollment or left ventricular ejection fraction (LVEF) less than 45% or less than the institutional lower limit of normal (whichever is higher) within 6 months prior to enrollment

7. Have cardiac conduction abnormalities as follows:

   a. QTcF >450 msec on the average of 3 serial baseline ECGs (using the QTcF formula); congenital long QT syndrome, or a known family history of long QT syndrome; or inability to determine the QTcF

   b. Presence of a complete left bundle branch block

   c. Use of a ventricular pacemaker

   d. History of clinically significant (as determined by the treating physician) atrial arrhythmia

   e. Resting bradycardia <50 beats per minute

   f. Any history of ventricular arrhythmia

8. Are taking medications with a known risk of Torsades de Pointes or that have the potential to prolong the QT interval (Appendix A), unless the medication can be discontinued or be substituted by another without the risk.

9. Are taking medicines that are strong CYP3A4 inhibitors, unless the medication can be discontinued or be substituted by another that is not an inhibitor (Appendix B)

10. Are taking medicines that are strong CYP3A4 inducers, unless the medication can be discontinued or be substituted by another that is not an inducer (Appendix B)

11. Have uncontrolled hypertension (i.e., >150 and >90 mmHg for SBP and DBP, respectively). Patients with hypertension should be under treatment at study entry to ensure blood pressure control. Those requiring 3 or more antihypertensive medications should be discussed with the medical monitor.

12. Have poorly controlled diabetes defined as HbA1c values of > 7.5%. Patients with preexisting, well-controlled, diabetes are not excluded.

13. Have uncorrected hypokalemia or hypomagnesemia.

14. Have active central nervous system (CNS) disease as evidenced by cytology or pathology. In the absence of clinical CNS disease, lumbar puncture is not required. A history of CNS involvement itself is not an exclusion if the CNS has been cleared of disease with a documented negative lumbar puncture.

15. Have a significant bleeding disorder unrelated to CML.

	16. Have a history of thrombophilia (eg, Protein C deficiency) 17. Have a history of alcohol abuse. 18. Have a history of acute pancreatitis within 1 year of study entry or history of chronic pancreatitis. 19. Have history of malabsorption syndrome or other gastrointestinal condition that could affect oral absorption of study drug. 20. Have a history of a different malignancy, other than cervical cancer in situ or basal cell or squamous cell carcinoma of the skin, except if patient has been disease-free for at least 5 years, and are deemed by the investigator to be at low risk for recurrence of that malignancy. 21. Are pregnant or lactating. 22. Have undergone major surgery within 14 days prior to first dose of study treatment. Minor surgical procedures, such as catheter placement or bone marrow biopsy are allowed. 23. Have an ongoing or active infection. This includes but is not limited to the requirement for intravenous antibiotics. 24. Have any surgical or medical condition / illness that, in the opinion of the investigator, would compromise patient safety or interfere with the evaluation of the study drug. 25. Have hypersensitivity to the active substance in ponatinib and nilotinib or to any of the inactive ingredients listed in Section 14.9.1.1 for ponatinib and in Section 14.9.1.2 for nilotinib.
Approximate Number of Patients	For the phase 2 portion, the overall total enrollment will be approximately 75 patients; all patients will be enrolled to the ponatinib 15 mg dose. For the phase 3 portion, the overall total enrollment will be approximately 600 patients randomized in a 1:2:1 fashion with approximately 150 patients in the ponatinib 30 mg starting dose cohort (Cohort A), approximately 300 patients in the ponatinib 15 mg starting dose cohort (Cohort B), and approximately 150 patients in the nilotinib cohort (Cohort C). Based on accumulating data from the 15 mg cohort in phase 2, the sample size for the phase 3 portion may be amended.
Approximate Duration of Patient Participation	The duration of patient participation will be 60 months for all patients. Each patient will undergo a period of up to 3 weeks for screening prior to treatment. The duration of therapy will be determined by the patient's response and toxicity, and patients will remain on assigned study treatment for 60 months if they are responding.

Approximate Duration of Study	The estimated duration of the phase 2 portion of the study is approximately 68 months, including 8 months for enrollment and 60 months of treatment/follow-up.
	
	The estimated duration of the phase 3 portion of the study is approximately 84 months (7 years), including 24 months for enrollment and 60 months of treatment/follow-up.
	
	The estimated duration of the study overall (both phases) is approximately 104 months, consisting of:
	
	• Approximately 20 months for phase 2 until the primary endpoint:
	  ○ 8 months for enrollment, and
	  ○ 12 months for treatment/follow-up to the primary endpoint, followed by
	• 84 months for phase 3 up to the end of the study:
	  ○ 24 months for enrollment, and
	  ○ 60 months of treatment/follow-up to the end of the study.
	
	Patients in both phases will be followed up to 60 months as defined in the protocol after they are evaluated for the primary endpoint at 12 months; however, enrollment in phase 3 will begin after patients in phase 2 are evaluated for the primary endpoint at 12 months.
	
	The overall study design may be modified based on the data from phase 2 that will inform the phase 3 portion of the study.

Approximate Number of Study Centers	Approximately 90 centers; multi-national.
Dosage and Administration	For the phase 2 portion, all patients will receive ponatinib 15 mg once daily (QD). Patients will have their daily dose of ponatinib reduced to 10 mg upon achievement of response as defined in Section 14.2.1. For the phase 3 portion, patients will be randomized to receive once daily oral administration of 1 of 2 starting doses of ponatinib: 30 mg (Cohort A), 15 mg (Cohort B), or twice daily oral administration of 400 mg of nilotinib (Cohort C) in a 1:2:1 ratio for Cohorts A, B, and C, respectively. Patients in Cohort A will have their daily dose reduced to 15 mg upon achievement of response as defined in Section 14.2.1, and patients in Cohort B will have their daily dose reduced to 10 mg upon achievement of response as defined in Section 14.2.1. The dose of nilotinib will not be adjusted based on response. Dose interruptions or reductions should be implemented for patients who experience treatment-related adverse events in phase 2 and in all 3 cohorts in phase 3, upon clinical judgment of the investigator. Guidelines for management of treatment-related adverse events are described in Section 14.4. For the phase 3 portion with nilotinib as the comparator, the current SmPC for Tasigna (nilotinib) should be used as the reference safety information for the nilotinib drug.
Concomitant Treatment	Medical or surgical treatment necessary for the patient's well-being is permitted. Where appropriate, patients may be treated with hematopoietic growth factors for limited times. Both ponatinib and nilotinib are associated with the potential for AOEs whereas ponatinib is also associated with potential for VTEs. Attention should be paid to appropriate medical management of conditions that contribute to risk of AOEs and VTEs. *Treatment of Hypertension*

	Hypertension (HTN) may contribute to risk of arterial occlusive events. Patients who have HTN should be managed appropriately before initiating treatment. During study treatment, blood pressure should be monitored and elevations managed. Hypertension should be treated to achieve a goal of <150/90 mmHg. Initial antihypertensive treatment should generally include a thiazide-type diuretic, calcium channel blocker, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker (James et al, 2014). Specific management of an individual patient should be determined by the treating physician. Study treatment should be temporarily interrupted if HTN is not medically controlled. Patients may require urgent clinical intervention for HTN associated with confusion, headache, chest pain, or shortness of breath. *Treatment of Diabetes* Patients with diabetes are at increased risk of experiencing arterial occlusive events. Initiation of or modifications to diabetic care should be considered in patients receiving study treatment who have elevated glucose levels or evidence of prior elevated glucose levels (eg, HbA1c). The American Diabetes Association guidelines should be followed, and diabetes treatment and lifestyle intervention (including but not limited to weight loss, decreased fat intake, calorie restriction, increased physical activity, and smoking cessation) should be started in any patient with fasting glucose >130 mg/dL (7.2 mmol/L) and/or HbA1c ≥7% (Diabetes Prevention Program Research Group, 2002; American Diabetes Association, Position Statement 2013). *Prohibited Treatments* The following concurrent medications and treatments are prohibited: • Other anticancer therapies, including other TKIs • Other investigational drugs or devices • Medications with a known risk of Torsades de Pointes or that prolong the QTcF interval (Appendix A) • Strong CYP3A4 inhibitors (Appendix B) • Strong CYP3A4 inducers (Appendix B) • Herbal preparations or related over-the-counter preparations containing herbal ingredients • Stem cell transplantation Elective surgery requiring inpatient care should be postponed until study completion if possible.
Efficacy Evaluation	MMR rates, other molecular response rates, cytogenetic response rates, hematologic response rates, and disease progression will be assessed according to standard criteria using the following measures: • BCR-ABL1 transcript assessment to determine molecular responses • Bone marrow aspirates for assessment of cytogenetic responses • Complete blood count for assessment of hematologic responses • Survival follow-up All patients remaining on study treatment will be followed for 60 months unless they withdraw sooner.

Safety Evaluation	Safety will be assessed by routine physical and laboratory evaluations, ECGs, and ECHOs. Adverse events will be recorded and the severity graded according to the NCI CTCAE v4.0. Baseline CML-related signs and symptoms will be recorded as AEs during the study if they worsen in severity or increase in frequency. All patients receiving at least one dose of study drug will be considered evaluable for safety. AEs and SAEs will be summarized for treatment-emergent adverse events (TEAEs) and all AEs will be listed. The number and percentages of patients who develop AOEs and VTEs will be summarized for each cohort; the primary analysis of arterial occlusive events and venous thromboembolic events will be an exposure-adjusted incidence rate. AOEs and VTEs will be categorized as follows: ● Arterial occlusive events i. Cardiovascular occlusive events ii. Cerebrovascular occlusive events iii. Peripheral vascular occlusive events ● Venous thromboembolic events
Exploratory Biomarker Evaluation	CCI [redacted]
Quality of Life and Health Outcomes Evaluation	Patients will complete the EuroQoL EQ-5D-5L and the FACT-Leu questionnaires at various times throughout the study.
Statistical Analysis	**Efficacy Analyses** **Phase 2:** Interim analyses will be performed after 50 patients reach 6 months of treatment. A sample size of 50 patients will distinguish a favorable ≤ 1% BCR-ABL1^{IS} by 6 month rate of 50% from a null or an uninteresting ≤ 1% BCR-ABL1^{IS} rate of 25%, with a nominal 96% power and a 2-sided type I error rate of 0.05 (equivalent to a 2-sided 0.025) using an exact binomial test. At the interim analysis, the CI for ≤ 1% BCR-ABL1^{IS} will be calculated. In the PACE (AP24534-10-201) trial, molecular responses at early time points were shown to be predictive of deeper molecular responses at later time points. Therefore, it is expected that ≤ 1% BCR-ABL1^{IS} by 6 months is expected to be a good surrogate for the primary endpoint of this study - MMR by 12 months. If there are fewer than 20 ≤ 1% BCR-ABL1^{IS} responders at the interim analysis, consideration may be given to terminating the study. Final analyses will be performed after all 75 patients reach 12 months of treatment. A sample size of 75 patients will distinguish a favorable MMR by 12 month rate of 40% from a null or an uninteresting MMR rate of 25%, with a nominal 80% power and a 2-sided type I error rate of 0.05 (equivalent to a 2-sided 0.025) using an exact binomial test. Using the 25% boundary for MMR, 27 or more MMR responders will be needed for a lower limit of the 2-sided exact 95% CI for the MMR rate to exceed 25%. **Phase 3:** Based on accumulating data from the 15 mg cohort in phase 2, the phase 3 design (including number of ponatinib cohorts) and/or sample size may be amended prior to enrollment of patients into the phase 3 portion of the study. The primary analysis of the primary endpoint will be performed using a stratified Cochran Mantel-Haenszel (CMH) test. The study will be stratified by age at baseline

(≥60 versus <60 years) and best response to prior imatinib therapy (CCyR or ≤ 1% BCR-ABL1^{IS} or better, yes/no) to compare the MMR rate by 12 months between patients receiving either dose level of ponatinib (initial dose: 30 mg QD or 15 mg QD) and patients receiving nilotinib (initial dose: 400 mg BID) and will follow a testing procedure to ensure an overall 2-sided Type I error rate of <0.05. An efficacy interim analysis is planned after the first 300 randomized patients have at least 12 months of follow-up. To maintain an overall Type I error rate of 0.05 (2-sided), an O'Brien-Fleming approach will be used which requires a 2-sided p-value <0.0052 at the interim (at 50% of information time). Thus, with 2 treatment comparisons significance will be declared for any arm where the 2-sided p-value is <0.0026 . For each dose comparison, if this boundary is not crossed at the time of the interim analysis, then the primary analysis will be conducted 12 months following the last patient randomized. A Bonferroni procedure will be used to adjust for comparisons of Cohorts A and B to Cohort C, with a dose considered significant if the 2-sided p-value is <0.024.

The primary analysis will be based on the Full Analysis Set (all patients randomized to a treatment group for whom a BCR-ABL1^{IS} ratio can be determined at baseline). A sensitivity analysis of the primary endpoint will be performed on the ITT population, with patients not evaluable treated as nonresponders.

The following patients will be analyzed as responders in the primary analysis:

- Patients who meet the criteria for MMR by 12 months after randomization

All other patients will be analyzed as non-responders in the primary analysis, including randomized patients without follow up and any patients who meet the criteria for MMR at study entry.

Comparisons of molecular key secondary endpoints and cytogenetic key secondary endpoints will be performed separately. Analyses of molecular key secondary endpoints will be performed on the Full Analysis Set. Analyses of cytogenetic key secondary endpoints will be performed on the ITT population. For each dose comparison (within a given set of key secondary endpoints) that is significant in the primary analysis, formal statistical comparisons of key secondary endpoints will be performed using a closed testing procedure according to the ranking below and will take place only if comparisons of all other secondary efficacy endpoints with a smaller rank are significant at the 2-sided 0.025 level (molecular endpoints and cytogenetic endpoints will be tested separately, thus the significance level has been halved). Note that at some analysis time points not all key secondary endpoints will be mature (eg, molecular key secondary endpoints will not be mature at interim analysis or 12 month analysis – see Section 16.5.3.3 for the statistical handling of these key secondary endpoints). Each sequence of key efficacy endpoints will be tested separately for each treatment comparison (Cohort A versus Cohort C, Cohort B versus Cohort C), within the sets of molecular and cytogenetic endpoints, respectively.

For the primary endpoint and secondary efficacy endpoints, subgroup analyses will be performed by baseline potential prognostic factors when warranted based on numbers of patients in subgroups. Subgroups may include:

- Age
- Gender
- Race
- Geographic region (North America, Europe, Other)
- T315I mutation history (Yes, No)
- Best response to prior imatinib therapy (CCyR, ≤ 1% BCR-ABL1^{IS} or better)
- Other disease-related prognostic factors

	Safety Analyses: All patients receiving at least 1 dose of study drug will be considered evaluable for safety. Safety analyses will be performed based on the treated population. Analyses will also be performed on adverse events of special interest (AESIs); further detail will be outlined in the Statistical Analysis Plan. Patients will be analyzed for safety according to the treatment they received. The AE incidence rates, as well as the frequency of occurrence of overall toxicity, categorized by toxicity grades (severity) will be described for each treatment arm. Listings of laboratory test results will also be generated, and descriptive statistics summarizing the changes in laboratory tests over time will be presented. Exposure to study drug over time will also be summarized. **Quality of Life / Health Outcomes Analysis:** Means and medians of raw scores of the EQ-5D-5L and FACT-Leu patient-reported outcome questionnaires will be summarized for each treatment group by time point, overall, and for each domain. **Sample Size Determination - Phase 2:** The primary endpoint for the phase 2 portion of the study will be MMR rate by 12 months. A sample size of 75 patients will distinguish a favorable MMR by 12 month rate of 40% from a null or an uninteresting MMR rate of 25%, with a nominal 80% power and a 2-sided type I error rate of 0.05 (equivalent to a 2-sided 0.025) using an exact binomial test. **Sample Size Determination - Phase 3:** Based on accumulating data from the 15 mg cohort in phase 2, the phase 3 design (including number of ponatinib cohorts) and/or sample size may be amended prior to enrollment of patients into the phase 3 portion of the study. The primary endpoint for the phase 3 portion of the study will be MMR rate by 12 months. The primary analysis of the primary endpoint of MMR will be performed using a 2-sided alpha = 0.024 for each comparison. A sample size of 150 patients each in Cohort A and C (ponatinib 30 mg and nilotinib, respectively) will distinguish a favorable MMR rate of 45% for ponatinib from a null or an uninteresting MMR rate of 25% for nilotinib with a nominal 90% power to detect an improvement in MMR of 20%. The sample size of 300 patients in Cohort B and 150 patients in Cohort C will distinguish a favorable MMR rate of 40% for ponatinib from a null or an uninteresting MMR rate of 25% for nilotinib with approximately 80% power to detect an improvement in MMR of 15%.
Rationale for Number of Patients	The total number of patients planned to be enrolled in this study is based on the sum of the individual cohorts described in the statistical considerations (675 patients). Based on accumulating data from the 15 mg cohort in phase 2, the phase 3 design (including number of ponatinib cohorts) and/or sample size may be amended prior to enrollment of patients into the phase 3 portion of the study.

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6 LIST OF ABBREVIATIONS

Abbreviation	Term
ABL	Abelson
AE	adverse event
AESI	adverse event of special interest
ALL	acute lymphoblastic leukemia / acute lymphocytic leukemia
ALT	alanine aminotransferase
AML	acute myelogenous leukemia / acute myeloid leukemia
ANC	absolute neutrophil count
AOEs	Arterial occlusive events
AP	accelerated phase
ARIAD	ARIAD Pharmaceuticals, Inc.
AST	aspartate aminotransferase
AUC	area under the curve
β-HCG	beta-human chorionic gonadotropin
BCR	Breakpoint Cluster Region
BCR-ABL1	Breakpoint Cluster Region-Abelson
$BCR\text{-}ABL1^{IS}$	BCR-ABL transcript level as measured by the International Scale
BID	twice daily
BM	bone marrow
BP	blast phase
BUN	blood urea nitrogen
CBC	complete blood count
CcyR	complete cytogenetic response
CHF	congestive heart failure
CHR	complete hematologic response
CI	confidence interval
C_{max}	maximum plasma concentration
CML	chronic myelogenous leukemia / chronic myeloid leukemia
CP	chronic phase
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
cTn	cardiac troponin
CYP	cytochrome P450
DLT	dose-limiting toxicity
EC	Ethics Committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EMA	European Medicines Agency
FACT-Leu	Functional Assessment of Cancer Therapy – Leukemia
FDA	Food and Drug Administration (United States)
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
HR-QoL	health-related quality of life
HSCT	hematopoietic stem cell transplantation
HTN	hypertension
IB	investigator brochure
ICMJE	International Committee of Medical Journal Editors
INR	International Normalized Ratio
IRB	Institutional Review Board

Abbreviation	Term
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LV	left ventricular
LVEF	left ventricular ejection fraction
MCyR	major cytogenetic response
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MMR	major molecular response
MR	molecular response
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute (of the United States)
OS	overall survival
PCR	polymerase chain reaction
PCyR	partial cytogenetic response
PFS	progression-free survival
Ph+	Philadelphia chromosome positive
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
QD	once daily
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)
R/I	resistant or intolerant
SAE	serious adverse event
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TIA	transient ischemic attack
TKI	tyrosine kinase inhibitor
TLS	tumor lysis syndrome
ULN	upper limit of normal
URL	upper reference limit
VTEs	Venous thrombotic/embolic events
WBC	white blood cell

7 DEFINITIONS OF TERMS

Term	Definition
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 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*.
Data Monitoring Committee	An independent committee consisting of 3 to 5 members not associated with the conduct of the study. The *data monitoring committee* will be responsible for evaluating the results of safety and efficacy interim analyses and will make recommendations to the sponsor on the conduct of the study.
Cycle	For the purposes of this study, a *cycle* consists of 28 days and is equivalent to a month in the measurement of study endpoints.
End-of-Treatment	The *end of treatment* occurs at the last dose of study treatment or when the investigator and patient decide that the patient will receive no further study treatment, whichever occurs later.
End-of-Study	The *end-of-study* (completion) date is when all patients have completed all study visits or have otherwise discontinued from the study.
Enrolled Patient	An *enrolled patient* is a patient who has signed the informed consent form, completed all screening evaluations, and has been randomized to a treatment group.
Ethics Committee	Throughout this document the term *Ethics Committee* (EC) refers to all appropriate properly constituted committees or boards recognized by the appropriate regulatory agencies for approving clinical studies. These include independent EC and Institutional Review Boards.
Evaluable for Safety	Any patient who receives study drug is considered *evaluable for safety* analyses.
Follow-up Period	The *follow-up period* for survival begins at the end of treatment and continues until patient contact discontinues.
Institutional Review Board	Throughout this document the term *Institutional Review Board* (IRB) refers to all appropriate properly constituted committees or boards recognized by the appropriate regulatory agencies for approving clinical studies. These include independent ECs and IRBs.
Patient	Throughout this document the term *patient* refers to a patient in this clinical research study.
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 Rules Governing Medicinal Products in the European Union; Ministry of Health, Labor, and Welfare (MHLW): Ethical Guidelines for Clinical Research (Japan); MHLW: Good Clinical Practice Guidelines (Japan); Japan Pharmaceuticals Affairs Law; the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice; and the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Patients.
Regulatory Agency	Throughout this document the term *regulatory agency* refers to all appropriate health and regulatory agencies. These may be international, national, or local and may include but not be limited to Ministry of Health, Labor, and Welfare (Japan), Pharmaceuticals and Medical Devices Agency (PMDA), European Medicines Agency (EMA), and the Food and Drug Administration (FDA; United States).
Sponsor	Throughout this document the term *sponsor* refers to all applicable departments within ARIAD Pharmaceuticals, Inc., or its designee.
Study Reference Manual	In the context of this study, *Study Reference Manual* is a general term for the information provided to sites on technical aspects of the study.

Term	Definition
Study Drug	A s*tudy 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 drugs are ponatinib (investigational medicinal product) and nilotinib (active control).
Study Start Date	The *study start date* is the date that the first patient signs the informed consent form.
Study Steering Committee	The *study steering committee* consists of clinician experts and sponsor representatives. The committee will be responsible for evaluating the results of safety and efficacy analyses and will make recommendations to the sponsor on the conduct of the study.
Treatment Period	The *treatment period* is from time of first dose until 30 days past last dose.

8 INTRODUCTION

This protocol describes a phase 2/3, open-label study of ponatinib for the treatment of patients with chronic myeloid leukemia (CML) in chronic phase (CP) whose imatinib therapy has failed. The phase 2 portion of the study will consist of a single treatment arm in which all patients will receive 15 mg ponatinib once daily. The goal of the phase 2 portion of this study is to generate efficacy and safety data to inform the design and sample size of the phase 3 portion of this study. In the phase 3 portion of the study, patients will be randomized to one of 2 doses of ponatinib (30 mg [Cohort A] and 15 mg [Cohort B] once daily) or nilotinib (400 mg twice daily; Cohort C). The goal of the phase 3 portion of this study is to test the hypothesis that ponatinib will be efficacious and safe in treating second-line CP-CML patients, that it will be superior to nilotinib, that each of the starting doses will demonstrate the continued efficacy of ponatinib, and that the dose reduction strategy will lessen arterial occlusive complications. While ponatinib is approved in the United States (US) and the European Union (EU) for patients who have become resistant or intolerant to available treatments [Iclusig® (ponatinib) Package Insert, 2016; Iclusig® (ponatinib) Summary of Product Characteristics, 2016], there is a strong rationale for testing ponatinib in patients who have become resistant after initial imatinib therapy.

8.1 Unmet Need in Second-Line CP-CML Therapy

Targeted therapy of Philadelphia chromosome-positive (Ph+) CML using the tyrosine kinase inhibitor (TKI) imatinib has been one of the most striking achievements in modern cancer medicine. Most patients with newly diagnosed CML are initially treated with an imatinib regimen with good results (Henk et al, 2015). However, 30% to 50% of all newly diagnosed CP-CML patients who are treated in the first-line setting with imatinib are in need of another treatment, either because they become resistant to imatinib (20%-25%) or because they become intolerant of imatinib (15%-20%) (Baccarani et al, 2009). Patients who experience failure of imatinib are treated second-line with available second generation agents, namely nilotinib and dasatinib [Tasigna® (nilotinib) Summary of Product Characteristics, 2014; Sprycel® (dasatinib) Summary of Product Characteristics, 2015, Sprycel® (dasatinib) Package Insert, 2010; Tasigna® (nilotinib) Package Insert, 2010]. In the US, an additional second generation TKI, bosutinib, may also be considered [Bosulif® (bosutinib) Package Insert, 2012]. Ponatinib may be an option if failure is the result of the T315I mutation [Iclusig® (ponatinib) Package Insert, 2016; Iclusig® (ponatinib) Summary of Product Characteristics, 2016].

A review of efficacy in the second-line setting demonstrates that there is potential for improvement. Major cytogenetic response (MCyR) rates in second-line CP-CML range from 51% with nilotinib therapy (n=321) (Nilotinib SmPC, 2016) to 62% in dasatinib treated patients (n=387) indicating that second-line therapy initially fails to achieve a response in a substantial fraction of patients. Additionally, none of the available second-line agents have activity against all of the known mutants and the T315I mutation is refractory to all TKIs with the exception of ponatinib.

Thus, both with regard to response rates and activity against resistant mutants, an unmet need remains in many patients who fail first-line TKI therapy. Ponatinib offers the potential to improve upon existing second-line therapy as it is the TKI with the most potent activity against BCR-ABL1, has activity against all resistant single mutants, and is effective in patients who have failed second-line treatments.

8.2 Ponatinib Background

8.2.1 Preclinical Summary

Ponatinib is a novel, synthetic, orally active TKI specifically designed to optimally inhibit native BCR-ABL1. It is also active against mutated forms of the protein that can arise during treatment with other TKIs and cause resistance, including the T315I gatekeeper mutant. Pharmacokinetic analysis of samples from the ongoing phase 1 clinical study (AP24534-07-101) showed that the threshold for pan-BCR-ABL1 activity is surpassed with ≥15 mg once daily dosing (C_{max}) and with ≥30 mg once daily (steady-state trough).

8.2.2 Ponatinib Use in Refractory CP-CML patients

The phase 1 study of ponatinib (AP24534-07-101) is a dose escalation study in 81 patients with refractory hematologic malignancies (65 with Ph+ leukemia) designed to determine the recommended phase 2 dose (RP2D) and assess anti-leukemic activity of ponatinib. Doses from 2 mg to 60 mg were investigated. The 45 mg daily dose was chosen as the recommended phase 2 dose and was determined to be the maximum tolerated dose (MTD). With a median follow-up of 49.9 months, MCyR, MMR, and MR4.5 were achieved by 31/43 (72.1%), 24/43 (55.8%), and 12/43 (28%) CP-CML patients, respectively. Median dose intensity was 28.3 mg daily for the CP-CML population. The most common treatment-emergent AEs (TEAEs) (≥40%) were rash (49.4%), nausea (45.7%), abdominal pain (44.4%), fatigue (44.4%), and headache (43.2%). Arterial occlusive events were observed: 13/43 (30%) CP-CML patients experienced cardiovascular occlusion, 4/43 (9%) experienced cerebrovascular occlusion, and 6/43 (14%) experienced peripheral vascular occlusive events. Pancreatitis was determined to be the dose-limiting toxicity (DLT).

The phase 2 study of ponatinib (AP24534-10-201, PACE) enrolled 449 patients with refractory CML or Ph+ ALL that was either resistant or intolerant to dasatinib or nilotinib or with the T315I mutation. The most recent 4-year data from this study confirmed that treatment with ponatinib continued to provide clinically meaningful responses. This includes the observation of maintenance of responses over time after dose reductions. Patients received a starting dose of 45 mg ponatinib daily and the median dose intensity was 29.4 mg daily (ranging from 3 to 45 mg daily) for CP-CML patients. The majority of CP-CML patients (252/270, 93%) enrolled in the study had been treated with 2 or more prior TKIs. With a median follow-up of 48.24 months, 55.4% of CP-CML patients achieved MCyR and 39.3% achieved MMR, and 85.7% remained in the primary end-point for ≥548 days at 30 mg. For maintenance of response over time after a dose reduction, among the 7 CP-CML patients who had dose reductions from 45 mg to 30 mg only, all patients maintained a MCyR for at least 548 days at the reduced dose. Of the 53 patients who had a dose reduction from 45 mg to 15 mg, 98.1% maintained a MCyR. Maintenance of responses was similar in the patients who had achieved a MCyR at the 30-mg dose and subsequently received a dose reduction to 15 mg. The median PFS and OS had not been reached for CP-CML patients, but the probability of remaining progression-free at 1, 2, 3, and 4 years was estimated as 79.2%, 68.3%, 60.5%, and 56.4%, respectively. The probability of overall survival at comparable times was estimated as 94.0%, 86.0%, 81.2%, and 76.8%, respectively. The most common TEAEs (≥40%) seen in the overall safety population (n=449) were thrombocytopenia (43.9%), abdominal pain (42.5%), and rash (41.6%). Continuing analyses of the phase 2 trial have demonstrated a higher cumulative incidence of arterial occlusive events

(including cardiovascular, cerebrovascular, and peripheral vascular events) observed with a longer follow-up, than reported at the time of the initial approval. Arterial occlusive events (AOEs)—including fatal myocardial infarction (MI), stroke, severe peripheral vascular disease, and the need for urgent revascularization procedures—have been reported in ponatinib-treated patients. The overall rate of arterial occlusive events after 48 months of follow-up was 23.2%, including the subsets of cardiovascular (12.5%), cerebrovascular (8.7%), and peripheral vascular (8.9%) events. The overall rate of venous thromboembolic events was 5.6%. Refer to the Investigator's Brochure for a complete evaluation of the ponatinib safety profile.

8.2.3 Ponatinib Results in Earlier Lines of Therapy

In an analysis of the phase 2 study, ponatinib elicits higher response rates in earlier lines of therapy. In particular, response rates observed in CP-CML patients who were previously treated with only one approved TKI (n=19) demonstrate 79% of patients achieved MCyR and 58% achieved MMR. This is in comparison to third-line CP-CML patients (n=98) in which 67% achieved MCyR and 42% achieved MMR. The MMR response in second-line patients is durable with 75% of patients estimated to remain in response at 1 year using Kaplan-Meier methodology.

In the ponatinib phase 2 study, second-line post- imatinib MMR rates at 45 mg were higher than those seen in nilotinib-treated patients post-imatinib, although the number of patients treated second-line with ponatinib treated is small (N=13) (Table 1).

Table 1 Fixed or Cumulative Molecular Response for Ponatinib and Nilotinib as Second-Line Therapy following Imatinib

Landmark	Response	Ponatinib After Imatinib	Nilotinib After Imatinib
At 3 months	MR1	9/13 = 69% (39%-91%) [4]	117/321 = 36% (31%-42%) [1]
	MR2	6/13 = 46% (19%-75%) [4]	61/321 = 19% (15%-24%) [1]
	MMR (MR3)	2/13 = 15% (1.9%-46%) [4]	
At 6 months	MR1	9/13 = 69% (39%-91%) [4]	124/321 = 39% (33%-44%) [1]
	MR2	8/13 = 61% (32%-86%) [4]	84/321 = 26% (21%-31%) [1]
	MMR (MR3)	4/13 = 31% (9.1%-61%) [4]	
By 12 months	MMR	8/13 = 61% (32%-86%) [5]	41/163 = 25% (19%-33%) [2]
By 24 months	MMR	9/13 = 69% (39%-91%) [4]	82/294 = 28% (23%-33%) [3]

[1] Giles et al; 2012 (1-6) [2] Hughes et al; 2009 [3] Kantarjian et al, 2011 [4] 06Jan2014 data cut [5] 09Nov2012 data cut
MR1= molecular response 1 (≤10% BCR-ABL1^{IS}); MR2= molecular response 2 (≤1% BCR-ABL1^{IS}); MR3= molecular response 3(≤0.1% BCR-ABL1^{IS}); MMR= major molecular response (≤0.1% BCR-ABL1^{IS})

Ponatinib (45 mg once daily) was also evaluated in newly diagnosed CP-CML patients in the phase 3 study (AP25434-12-301, EPIC) compared to imatinib (400 mg twice daily). In response to an increasing accumulation of arterial occlusive events throughout the clinical program, the phase 3 study was terminated prior to completion. Upon study termination, 307 patients were enrolled in the study (155 in ponatinib arm, 152 in imatinib arm; 58% of target enrollment). At that time, ponatinib-treated patients had a median follow-up of 5.0 months (range 0.03-17.6 months) and imatinib-treated patients had a median follow-up of 5.3 months (range 0.5-14.1 months). Preliminary findings based on data up until the early termination suggest there are differences in efficacy between ponatinib and imatinib therapy, favoring ponatinib, as measured by MMR at 3, 6, and 9 months and by MR4 and MR4.5 for all time points through 12 months. With 288 patients (148 ponatinib, 140 imatinib) with a post-baseline assessment of molecular

response, the rates of MMR at any time (41% vs. 18%), MR4 at any time (21% vs. 1%), and MR4.5 at any time (15% vs. 0%) were significantly higher for patients on the ponatinib arm than the imatinib arm (all p-values <0.001).

8.3 Selection of Ponatinib Dose

This clinical study will test two modulations of ponatinib dose: lower starting doses and dose reduction after achievement of response (as described below and in Section 10.2). The data that support these approaches derive from univariate and multivariate analyses of the relationship of dose with efficacy and safety, along with analyses of the effects of dose reductions on response and safety.

The impact of dose on achievement of MCyR in patients with CP-CML has been evaluated using a multivariate analysis of data from the phase 2 study adjusting for covariates and an analysis of response by dose tertile. Both analyses show that increasing dose intensity is associated with higher response rates in this predominantly fourth-line population of CP-CML patients. The multivariate analysis indicates that dose intensity is associated with achievement of MCyR by 12 months in CP-CML patients with an odds ratio of 3.222 (p<0.0001). An analysis of CP-CML patients shows a decrease in MCyR and MMR from the highest dose-intensity tertile to the lowest dose-intensity tertile (Table 2). Nevertheless, response rates are still high in the lowest tertile, with the understanding that this is not a second-line patient population.

Table 2 Response Rate by Dose Tertile in CP-CML Patients (AP24534-10-201)

Dose Intensity (mg/day)	Response (%)		
	MCyR	CCyR	MMR
>40 (n=80)	76%	70%	56%
>26 to ≤40 (n=79)	68%	54%	48%
≤26 (n=79)	42%	30%	22%

Data extraction date: 03 September 2013. N restricted to the subset of patients with at least 3 months of follow-up (to exclude the impact of patients who dropped out with insufficient exposure to see a response).
CCyR=complete cytogenetic response, MCyR=major cytogenetic response, MMR=major molecular response.

Multivariate analyses on data from the phase 2 study showed increasing dose intensity correlated with an increased probability of experiencing AEs. The relationship between dose intensity and arterial occlusive events was examined using multivariate analysis with an expanded set of covariates with a minimum of 24 months of follow-up. All modeling showed that dose intensity (up to the time of the events) was statistically-significantly associated with an increase in event rate in univariate models, and became more significant when adjusting for covariates in multivariate models. Additionally, dose reduction by 15 mg/day was predicted to lead to an approximate 33% risk reduction in the incidence of arterial occlusive events.

Analyses in patients who underwent dose reduction due to AEs show that patients can maintain response on doses lower than 45 mg daily. Of patients who achieved response at 45 mg and subsequently had their dose reduced to either 30 mg or 15 mg, 6/7 (85.7%) and 52/53 (98.1%) maintained MCyR, respectively, compared to 15/21 (71%) patients who did not dose reduce. Patients who had achieved a MCyR at the 30 mg dose and received a dose reduction to 15 mg showed similar maintenance of responses, with 7 patients maintaining a MCyR for ≥ 1095 days at the reduced dose of 15 mg. Similar results were obtained with regard to patients who achieved

MMR. Among patients who achieved MMR at 45 mg, 4/5 (80.0%) and 36/40 (90.0%) patients who dose reduced to 30 mg or 15 mg, respectively, maintained their response while 11/18 (61.1%) patients who did not dose reduce, maintained their response.

Taken together, these data underpin the rationale for investigating lower doses of ponatinib in conjunction with dose reduction following response. This study will employ starting doses of 15 mg (in phase 2) and 30 mg and 15 mg (in phase 3) to achieve response and then reduce dosing to lower the risk of AEs while maintaining response.

8.4 Selection of Nilotinib as a Comparator

Nilotinib is approved in the US and EU for adult CP-CML patients who are resistant to or intolerant of prior therapy that included imatinib [Gleevec® (imatinib) Package Insert, 2012; Glivec® Summary of Product Characteristics, 2015). The approved dose in both the US and the EU is 400 mg twice daily for this indication. Both NCCN (O'Brien et al, 2014) and ELN (Baccarani et al, 2013) guidelines recommend consideration of the use of nilotinib in patients initially treated with imatinib whose disease develops resistance to therapy.

The efficacy of nilotinib as a second-line therapy post imatinib in studies with long follow-up has been clearly established and extensively studied. Data in a phase 2 study of CP-CML patients whose disease was resistant or intolerant to imatinib demonstrated that 59% (190/321) of CP-CML patients achieved MCyR by 24 months (Giles et al, 2013). At 48 months, PFS and OS in CP-CML patients were predicted to be 57% and 78%, respectively. Data regarding MMR rates in the second-line population are less certain. The rates of MMR by 12 months have been estimated to be 25% (Hughes et al, 2009) and by 24 months 28% (Kantarjian et al, 2011) but these analyses involve subset analyses of patients with available samples in the nilotinib second-line experience.

Like ponatinib, nilotinib-treated patients have experienced peripheral vascular events. At 5 years of follow up, 15.2% of newly diagnosed CP-CML patients treated with nilotinib experience arterial occlusive events (Note: this rate cannot be compared directly with ponatinib since individual event terms are not provided) (Tasigna® Package Insert, 2016; Tasigna® Summary of Product Characteristics, 2016). In both the ponatinib and nilotinib development programs, most of these patients had additional risk factors for cardiovascular disease. The use of nilotinib as a comparator thus offers the opportunity to compare these agents directly in a single patient population.

8.5 Selection of Endpoints

The depth of and time to molecular response is well correlated with clinical outcome, and this provides the rationale for utilizing MMR as a measure of outcome in the patient population studied here. Marin and colleagues have shown that a strong predictor of OS is the attainment of BCR-ABL1 transcript levels below 10% by 3 months after the initiation of therapy (Marin et al, 2012). This observation supports continued use of molecular response endpoints and suggests that the rapidity and depth of molecular response may be an important indicator of treatment success.

Time to achieve response is also important. In a study by the German CML Study Group of over 1,300 patients starting treatment with a TKI (Hanfstein et al, 2012), the estimated OS at 5 years for those who achieved a 1-log reduction in the first three months was 94%. For patients who had

a 2-log reduction at three months, the estimated survival was 97%. If patients didn't have this degree of early leukemia suppression, the estimated 5-year survival dropped to 87%.

In ponatinib-treated patients in the phase 2 study, molecular response at 3, 6, and 12 months had a significantly positive association with long-term PFS and OS. Patients who achieved MMR at 12 months had a PFS of 93% and OS of 100% at 2 years. This is in contrast to patients who did not achieve MMR at 12 months who had a probability of PFS of 74% and probability of OS of 93% at 2 years (Muller et al, 2014).

This benchmark of response is reflected in the ELN guidelines. The goals of therapy outlined are to achieve a 1-log reduction within the first 3 months of treatment, a 2-log reduction within the first 6 months, and a 3-log reduction (that is, MMR) within 12 months (Baccarani et al, 2013). This supports the choice of MMR by 12 months as the primary endpoint of this study.

8.6 Selection of Study Design

8.6.1 Phase 2

The single arm phase 2 portion of the study will estimate the efficacy, as measured by MMR rate by 12 months, of a 15 mg starting ponatinib dose, in patients with CP-CML following resistance to imatinib. The ponatinib dose chosen is based on the current molecular response rates with ponatinib therapy. A sample size of 75 patients will distinguish a favorable MMR by 12 month rate of 40% from a null or an uninteresting MMR rate of 25%, with a nominal 80% power and a 2-sided type I error rate of 0.05 (equivalent to a 2-sided 0.025) using an exact binomial test.

Interim analyses will also be performed after 50 patients reach 6 months of treatment during the phase 2 portion of the study. A sample size of 50 patients will distinguish a favorable $\leq 1\%$ BCR-ABL1^{IS} by 6 month rate of 50% from a null or an uninteresting $\leq 1\%$ BCR-ABL1^{IS} rate of 25%, with a nominal 96% power and a 2-sided type I error rate of 0.05 (equivalent to a 2-sided 0.025) using an exact binomial test. At the interim analysis, the CI for $\leq 1\%$ BCR-ABL1^{IS} will be calculated. Based on the observation from the phase 2 study of ponatinib (AP24534-10-201; PACE), $\leq 1\%$ BCR-ABL1^{IS} at 6 months is considered to be a good surrogate for the primary endpoint of this study - MMR by 12 months.

8.6.2 Phase 3

The phase 3 portion of this study will evaluate the superiority of a ponatinib dosing strategy compared with the current approved dosing regimen for nilotinib. The study will also compare arterial occlusive event rates by dose and treatment.

Two-thirds of the patients will have a minimum follow-up of at least 18 months at the time of the primary analysis and the data will enable the efficacy and safety comparison of ponatinib versus nilotinib. The safety profile will be further characterized by secondary analyses until all patients have reached the end of the study, which is planned to last 60 months.

Patients will be randomized 1:2:1 to 30 mg ponatinib QD (Cohort A), 15 mg ponatinib QD (Cohort B), or 400 mg nilotinib BID (Cohort C), taken orally. A sample size of 150 patients in each Cohort A and C (ponatinib 30 mg and nilotinib) will distinguish a favorable MMR rate of 45% for ponatinib from a null or an uninteresting MMR rate of 25% for nilotinib with a nominal 90% power to detect an improvement in MMR of 20%. The sample size of 300 patients in Cohort B and 150 patients in Cohort C will distinguish a favorable MMR rate of 40% for

ponatinib from a null or an uninteresting MMR rate of 25% for nilotinib with approximately 80% power to detect an improvement in MMR of 15%. Thus, the larger cohort size utilizing ponatinib at a lower dose will enable the detection of a smaller improvement in efficacy with adequate power.

8.6.2.1 Rationale for Phase 3 Design Based on Phase 2

Based on accumulating data from the 15 mg cohort and supportive clinical data evolving from additional studies highlighted below, the phase 3 design (including number of ponatinib cohorts) and/or sample size may be amended prior to enrollment of patients into the phase 3 portion of the study.

8.6.2.2 Rationale for Phase 3 Design Based on Additional Supportive Data

In addition to data from phase 2, evolving cumulative safety data from the OPTIC study will be evaluated to inform the design of the phase 3 portion of the study. OPTIC is an ARIAD-sponsored randomized, open-label, phase 2 study of ponatinib in patients with resistant CP-CML to characterize the efficacy and safety of a range of doses including 45, 30 and 15 mg.

Additionally, supportive clinical data evolving from the currently active phase 2 investigator initiated study conducted by *Gruppo Italiano Malattie EMatologiche dell'Adulto* (GIMEMA) evaluating the activity and risk profile of ponatinib at 30 mg QD in CP-CML (refer to ClinicalTrials.gov Identifier: NCT02398825 for further details) will be considered.

9 STUDY OBJECTIVES

9.1 Primary Objectives

Phase 2

The primary objective of the phase 2 portion of this study is to demonstrate the efficacy of ponatinib administered at a dose of 15 mg in patients with CP-CML who are resistant to imatinib, as measured by MMR by 12 months, with the goal of generating efficacy and safety data to inform the design and sample size of the phase 3 portion of this study.

Phase 3

The primary objective of the phase 3 portion of this study is to demonstrate the efficacy of ponatinib administered at 2 starting doses (30 and 15 mg QD) compared to nilotinib administered at 400 mg BID in patients with CP-CML who are resistant to imatinib, as measured by MMR by 12 months.

9.2 Key Secondary Objectives in Phase 2 and Each Cohort in Phase 3

The key secondary objectives of this study are:

- To characterize, according to each arm and ponatinib starting dose, the rate of AOEs and VTEs, AEs, and serious adverse events (SAEs).
- To characterize, according to each arm and ponatinib starting dose, the rate of cytogenetic responses and molecular responses other than MMR.

- To further characterize efficacy according to each arm and ponatinib starting dose, including time to response, duration of cytogenetic and molecular response, duration of therapy, progression free survival (PFS), overall survival (OS), and impact of dose escalation after loss of response (ponatinib cohorts only)

9.3 Other Secondary Objectives in Phase 2 and Each Cohort in Phase 3

Other secondary objectives of this study are:

- To characterize, according to each arm and ponatinib starting dose, the rate of discontinuation, dose reductions, and interruptions.
- To characterize, according to each arm and ponatinib starting dose, the rate of hematologic responses.

9.4 Exploratory Objectives

CCI [redacted]

10 INVESTIGATIONAL PLAN

10.1 Overall Study Design and Plan

This is a multi-center study to demonstrate the efficacy and safety of 15 mg ponatinib during the phase 2 portion, and a randomized comparison of two starting doses of ponatinib as compared to nilotinib during the phase 3 portion. Eligible patients must have CP-CML, be resistant to first-line imatinib treatment and not received any other TKI therapy.

During the phase 2 portion, all patients will receive ponatinib 15 mg QD. Upon achievement of major molecular response (MMR) as defined in Section 16.5.1.1, patients will have their daily dose of ponatinib reduced to 10 mg.

During the phase 3 portion, patients will be randomized to receive once daily oral administration of either 30 mg ponatinib QD (Cohort A), or 15 mg ponatinib QD (Cohort B), or 400 mg nilotinib BID (Cohort C). They will be randomized in a ratio of 1:2:1, respectively. The primary endpoint of MMR by 12 months is defined according to standard criteria as ≤0.1% BCR-ABL1/ABL1^{IS}. Upon achievement of MMR as defined in Section 16.5.1.1, patients in Cohort A will have their daily dose of ponatinib reduced to 15 mg and patients in cohort B will have their daily dose of ponatinib reduced to 10 mg. The dose of nilotinib for patients in Cohort C will not be adjusted based on response.

Ponatinib dose reduction upon achievement of MMR can also be implemented when an unscheduled response assessment is performed.

Treatment will continue until lack of response at 12 months is established, intolerance develops or response is lost. In the ponatinib arms (the ponatinib 15 mg group in the phase 2 portion and Cohorts A and B in the phase 3 portion), patients who achieve and then lose response after dose reduction for MMR may have their dose escalated to their initial dose and remain on study. In the nilotinib arm, Cohort C, patients who lose response will discontinue study treatment.

The study will assess hematologic response, cytogenetic response, and molecular response, as well as additional measures of efficacy including time to responses, and duration of responses by starting dose and after dose reduction. PFS and OS data will also be collected and analyzed. Adverse event rates and the rates of vascular occlusive events, in particular, will be measured. Assessments will be according to standard international criteria. The duration of patient participation will be 60 months for all patients, unless they withdraw prior to that based on the withdrawal criteria defined within the protocol.

10.1.1 Primary Endpoint in Phase 2 and Each Cohort in Phase 3

The primary endpoint for this study is major molecular response (MMR) by 12 months for each cohort.

10.1.2 Key Secondary Endpoints in Phase 2 and Each Cohort in Phase 3

The key secondary endpoints for this study are:

- Cytogenetic response rates:
  i. MCyR, as defined in Section 16.5.1.2, by 12 months
  ii. CCyR by 12 months
- Molecular response rates: ≤ 1% BCR-ABL1^{IS}, MR3/MMR, MR4, MR4.5 at 3-month intervals until end-of-treatment and MR1 (≤10% BCR-ABL1^{IS}) at 3 months
- Safety
  i. Arterial occlusive and venous thrombotic/embolic events in each cohort
  ii. AEs in each cohort
  iii. SAEs in each cohort
- Time to response
- Duration of response:
  i. ≤ 1% BCR-ABL1^{IS} and MMR at 3, 6, 9, and 12 months, and then at 3-month intervals until completion of treatment
  ii. MCyR at 12 and 24 months, by cytogenetic analysis
  iii. Duration of response in responders
  iv. Duration of therapy
- Progression-free survival
- Overall survival

10.1.3 Other Secondary Endpoints in Phase 2 and Each Cohort in Phase 3

Other secondary endpoints for this study include:

- Hematologic response rates: CHR
- Tolerability:

i. Discontinuation due to AEs in each cohort

ii. Dose reductions due to toxicity in each cohort

iii. Dose interruptions in each cohort

- Progression to AP- or BP-CML

10.1.4 Exploratory Endpoints

CCI

[redacted]

10.2 Description of Treatment

For the phase 2 portion, all patients will receive ponatinib 15 mg QD.

For the phase 3 portion, patients will be randomized to receive once daily oral administration of one of two starting doses of ponatinib: 30 mg (Cohort A), 15 mg (Cohort B), or twice daily oral administration of 400 mg of nilotinib (Cohort C) in a 1:2:1 ratio for Cohorts A, B, and C, respectively.

Treatment will continue until lack of response at 12 months is established, intolerance develops or response is lost, to a maximum of 60 months.

Mandatory dose reduction: Patients in Cohort A of the phase 3 portion will have their daily dose reduced to 15 mg upon achievement of MMR at 3, 6, 9, or 12 months (as defined in Section 16.5.1.1) or if they are in MCyR at 12 months (as defined in Section 14.2.1 and Section 16.5.1.2 or as a reduction of BCR-ABL1^{IS} to ≤ 1%). Patients in the phase 2 portion and in Cohort B of the phase 3 portion will have their daily dose reduced to 10 mg upon achievement of MMR at 3, 6, 9, or 12 months or if they are in MCyR at 12 months. Ponatinib dose reduction upon achievement of MMR can also be implemented when an unscheduled response assessment is performed. The dose of nilotinib for patients in Cohort C will not be adjusted based on response. The schedule for dose reduction is described in Section 14.2.

Dose reduction for adverse drug reactions: Dose interruptions or reductions should be implemented for patients who experience treatment-related AEs in all 3 cohorts, upon clinical judgment of the investigator. Guidelines for management of treatment-related AEs are described in Section 14.4.1, and guidelines for dose modifications for adverse drug reactions are described in Section 14.4.2.1.

Escalation for loss of response following dose reduction: Patients in the ponatinib arms who undergo dose reduction upon achievement of MMR or MCyR and who, with continued monitoring, lose MCyR may undergo dose escalation back to the starting dose at the discretion of the physician. The dose re-escalation schema is described in Section 14.2.2.

10.3 Randomization

In the phase 2 portion, all patients will receive ponatinib 15 mg QD.

In the phase 3 portion, patients will be randomized in a 1:2:1 ratio to receive either ponatinib in one of 2 starting doses or nilotinib.

Cohort A: 30 mg ponatinib QD with reduction to 15 mg at 3, 6, 9, or 12 months upon achievement of MMR.

Cohort B: 15 mg ponatinib QD with reduction to 10 mg at 3, 6, 9, or 12 months upon achievement of MMR.

Cohort C: 400 mg nilotinib BID.

A cycle of therapy will comprise 28 days of treatment, regardless of dose.

The randomization for phase 3 will be stratified based on the patient's baseline age (≥60 vs <60 years) and best response to prior imatinib therapy (CCyR or ≤ 1% BCR-ABL1^{IS} or better, yes/no). Specific instructions for randomization will be supplied in the Study Reference Manual. Randomization procedures should be performed following confirmation of eligibility. This study is open-label; patients, investigators, and the sponsor will know the identity of each patient's study treatment.

11 SELECTION OF STUDY POPULATION

11.1 Inclusion Criteria

All patients must take part in the informed consent process. This process is described in Section 12.1. Screening tests and procedures used to establish eligibility are outlined in Section 12.1, Table 3. Documentation from the screening period is required for each inclusion and exclusion criterion.

Patients must meet all of the following criteria in order to be eligible for the study:

1. Have CP-CML resistant to first-line imatinib treatment.
    a. The diagnosis of CML will be made using standard hematopathologic and cytogenetic criteria. CP-CML will be defined by all of the following:
        i <15% blasts in bone marrow
        ii <30% blasts plus promyelocytes in bone marrow
        iii <20% basophils in peripheral blood
        iv ≥100 × 10^9/L platelets (≥100,000/mm^3)
        v No evidence of extramedullary disease except hepatosplenomegaly
        vi No prior diagnosis of accelerated phase (AP) or blast phase (BP) CML
    b. Cytogenetic assessment must demonstrate the BCR-ABL1 fusion by presence of the t(9;22) Philadelphia chromosome.
        i Conventional chromosome banding must be performed
        ii A minimum of 20 metaphases must be assessable at entry. If < 20 metaphases are assessable, a real time PCR with > 1% of BCR-ABL1^{IS} is required to be eligible
        iii Variant translocations are not allowed

c. BCR-ABL1 transcript levels must be assessable using the International Scale (ie, patients must have either the b2a2 or b3a2 transcript type)

d. Resistance is defined as follows. Patients must meet at least 1 criterion.

i Three months after the initiation of therapy: No cytogenetic response (>95% Ph+) or failure to achieve CHR.

ii Six months after the initiation of therapy: BCR-ABL1^{IS} >10% and/or >35% Ph+.

iii Twelve months after the initiation of therapy: BCR-ABL1^{IS} >1% and/or Ph+ >0.

iv At any time after the initiation of therapy, the development of new BCR-ABL1 kinase domain mutation(s).

v At any time after the initiation of therapy, the development of new clonal evolution.

vi At any time after the initiation of therapy, the loss of CHR, the loss of CCyR, or the confirmed loss of MMR in 2 consecutive tests, one of which has a BCR-ABL1^{IS} transcript level of ≥1%.

[NOTE: The above criteria were adapted from Baccarani et al. 2013.]

2. Age ≥18 years old.
3. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
4. Have adequate renal function as defined by the following criterion:
   a. Serum creatinine ≤1.5 × upper limit of normal (ULN) for institution.
5. Have adequate hepatic function as defined by all of the following criteria:
   a. Total serum bilirubin ≤1.5 × ULN, unless due to Gilbert's syndrome.
   b. Alanine aminotransferase (ALT) ≤2.5 × ULN or ≤5 × ULN if leukemic infiltration of the liver is present.
   c. Aspartate aminotransferase (AST) ≤2.5 × ULN or ≤5 × ULN if leukemic infiltration of the liver is present.
6. Have normal pancreatic status as defined by the following criterion:
   a. Serum lipase and amylase ≤1.5 × ULN.
7. Have a negative pregnancy test documented prior to enrollment (for females of childbearing potential).
8. Agree to use a highly effective form of contraception with sexual partners from the time of randomization through at least four (4) months after the end of treatment (for female and male patients who are fertile).
9. Provide written informed consent.
10. Be willing and able to comply with scheduled visits and study procedures.
11. Have recovered from toxicities related to prior anticancer therapy to NCI CTCAE grade ≤1 except for alopecia or peripheral neuropathy.

11.2 Exclusion Criteria

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

1. Have previously been treated with any approved or investigational TKIs other than imatinib or treated with imatinib within 14 days prior to receiving study drug.
2. Have previously been treated with any anti-CML therapy other than hydroxyurea, including interferon, cytarabine, immunotherapy, or any cytotoxic chemotherapy, radiotherapy, or investigational therapy.
3. Underwent autologous or allogeneic stem cell transplant.
4. Are in ≤ 1% BCR-ABL1 (in phase 2) or in MMR (in phase 3).
5. Have a known history of T315I mutation in phase 3.
6. Have clinically significant, uncontrolled, or active cardiovascular disease, specifically including, but not restricted to:
    a. Any history of myocardial infarction (MI), unstable angina, cerebrovascular accident, or transient ischemic attack (TIA)
    b. Any history of peripheral vascular infarction, including visceral infarction
    c. Any history of revascularization procedure, including vascular surgery or the placement of a stent
    d. Any history of venous thromboembolism including deep venous thrombosis, superficial venous thrombosis, or pulmonary embolism, within 6 months prior to enrollment
    e. Congestive heart failure (New York Heart Association [NYHA] class III or IV) within 6 months prior to enrollment, or left ventricular ejection fraction (LVEF) less than 45% or less than the lower limit of normal per local institutional standards (whichever is higher) within 6 months prior to enrollment
7. Have cardiac conduction abnormalities as follows:
    a. QTcF >450 msec on the average of 3 serial baseline ECGs (using the QTcF formula); congenital long QT syndrome, or a known family history of long QT syndrome; or inability to determine the QTcF
    b. Presence of a complete left bundle branch block
    c. Use of a ventricular pacemaker
    d. History of clinically significant (as determined by the treating physician) atrial arrhythmia
    e. Resting bradycardia <50 beats per minute
    f. Any history of ventricular arrhythmia
8. Are taking medications with a known risk of Torsades de Pointes or that have the potential to prolong the QT interval (Appendix A), unless the medication can be discontinued or be substituted by another without the risk.

9. Are taking medicines that are strong CYP3A4 inhibitors, unless the medication can be discontinued or be substituted by another that is not an inhibitor (Appendix B).
10. Are taking medicines that are strong CYP3A4 inducers, unless the medication can be discontinued or be substituted by another that is not an inducer (Appendix B).
11. Have uncontrolled hypertension (i.e., >150 and >90 mmHg for SBP and DBP, respectively). Patients with hypertension should be under treatment at study entry to ensure blood pressure control. Those requiring 3 or more antihypertensive medications should be discussed with the medical monitor.
12. Have poorly controlled diabetes defined as HbA1c values of > 7.5%. Patients with preexisting, well-controlled, diabetes are not excluded.
13. Have uncorrected hypokalemia or hypomagnesemia.
14. Have active central nervous system (CNS) disease as evidenced by cytology or pathology. In the absence of clinical CNS disease, lumbar puncture is not required. A history of CNS involvement is not itself exclusionary if the CNS has been cleared of disease with a documented negative lumbar puncture.
15. Have a significant bleeding disorder unrelated to CML.
16. Have a history of thrombophilia (eg, Protein C deficiency).
17. Have a history of alcohol abuse.
18. Have a history of acute pancreatitis within 1 year of study entry or a history of chronic pancreatitis.
19. Have malabsorption syndrome or other gastrointestinal illness that could affect oral absorption of study drug.
20. Have a history of another malignancy, other than cervical cancer in situ, basal cell or squamous cell carcinoma of the skin, except if patient has been disease-free for at least 5 years, and are deemed by the investigator to be at low risk for recurrence of that malignancy.
21. Are pregnant or lactating.
22. Have undergone major surgery within 14 days prior to first dose of study treatment. Minor surgical procedures, such as catheter placement or bone marrow biopsy, are allowed.
23. Have an ongoing or active infection. This includes but is not limited to the requirement for intravenous antibiotics.
24. Have any surgical or medical condition or illness that, in the opinion of the investigator, would compromise patient safety or interfere with the evaluation of the study drug.
25. Have hypersensitivity to the active substance in ponatinib and nilotinib or to any of the inactive ingredients listed in Section 14.9.1.1 for ponatinib and in Section 14.9.1.2 for nilotinib.

12 STUDY PROCEDURES

12.1 Schedule of Events

Table 3 lists the screening and study procedures to be done through Cycle 12 for both the phase 2 and phase 3 portions of the study. Table 4 lists the procedures to be done after Cycle 12 through the end of both the phase 2 and phase 3 portions of the study. Unless otherwise specified, the timing in which Cycle 1 tests are performed should be repeated in later cycles. Cycle visit samples or activities should occur within 3 days of the scheduled study day unless otherwise noted in the Schedule of Events.

Please maintain a special awareness of the assessments of the primary and secondary endpoints.

The following describes the procedures/tests required for this study:

1 Screening Period Procedures

Screening tests and procedures are used to establish eligibility of the patient for the study. Patients must continue to maintain laboratory values within eligibility parameters if any given procedure or laboratory test is repeated prior to randomization.

All screening tests must be done within 21 days prior to randomization with the exception of the screening bone marrow (BM) aspirate (within 42 days) and screening pregnancy test (within 7 days of first dose of drug).

2 Informed Consent

All patients must take part in the informed consent process. During the consent process, the person obtaining consent must inform the patient of all elements of informed consent. Adequate time must be allowed for questions and for the patient to make a voluntary decision. No protocol-specific procedures are to be performed until the patient has signed and dated an Institutional Review Board (IRB)/Ethics Committee (EC) approved informed consent form. Each patient's participation in the study begins with the signing and dating of the informed consent form.

3 Randomization (Phase 3 Only)

Specific instructions for randomization will be supplied in the Study Reference Manual. Randomization procedures should be performed within the 21 day screening period following completion of eligibility assessments and just prior to the initiation of assigned dose cohort.

4 Medical/Surgical History and Demographics

Medical and surgical history and demographic information will be recorded. Medical and surgical history includes diagnoses, therapies, medical and surgical treatments, lifestyle factors, and family history.

Special attention should be paid to documenting risk factors for arterial cardiovascular cerebrovascular, peripheral vascular, and venous thromboembolic disease, and the history must include any history of ischemic heart disease (including angina, myocardial infarction, acute coronary syndrome, coronary revascularization procedures, etc.), valvular heart disease, congestive heart failure, arrhythmias, myocarditis, peripheral arterial occlusive disease (including claudication, distal extremity amputation, angioplasty, or revascularization procedure), stroke (including transient ischemic attacks [TIA], cerebral atherosclerosis,

revascularization procedures), diabetes mellitus, hypertension, hypercholesterolemia, hyperlipidemia, deep venous thrombosis, pulmonary embolism, any other coagulopathy (eg, protein S or protein C deficiency, anticardiolipin antibody), physical inactivity, obesity, and smoking. Note that a history of a prior myocardial infarction, unstable angina, stroke, transient ischemic attack, any ischemic infarct, or a revascularization procedure is exclusionary.

Family medical history will be collected and should include history of coronary artery disease, early death from myocardial infarction or cerebrovascular accident, sudden death, and bleeding or clotting diatheses in first-degree relatives. Demographic information consists of the patient's age, gender, race, and ethnicity (as allowed by local law and regulations).

5 Leukemia Diagnosis and Prior Cancer Therapy

Both the initial leukemia diagnosis and the current screening diagnosis must be recorded. Note: only patients currently in CP-CML and with no prior history of AP-CML or BP-CML are eligible. Prior 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 of or intolerance to each regimen. As described in Section 11.2, previous treatment with any approved or investigational TKIs other than imatinib or treatment with any anti-CML therapy other than hydroxyurea, including interferon, cytarabine, immunotherapy, or any cytotoxic chemotherapy, radiotherapy, stem cell transplant, or investigational therapy are exclusionary criteria.

6 BCR-ABL1 Mutation History

At the time of screening, prior and current history of any known BCR-ABL1 mutations must be recorded.

7 Vital Signs

Vital signs are temperature, pulse, respiratory rate, and blood pressure (when the patient is seated).

8 Complete Physical Exam and ECOG Performance Status

A complete physical examination, including measurement of weight, must be performed at screening; at Cycle 1, Day 1 prior to the first administration of study drug; and at the End-of-Treatment visit. All physical examinations should address the presence or absence of hepatomegaly and splenomegaly, which must be recorded. The extent of the physical examination should be consistent with the medical history and the patient's underlying disease. ECOG performance status should be evaluated during each physical examination. Following the physical examination for Cycle 1, Day 1—with the exception of the End-of-Treatment visit—all subsequent physical examinations (to be performed on Days 15 and 28 of Cycle 1 and Day 28 of Cycles 2, 3, 6, 9, 12, 18, and 24 and every 6 months thereafter as indicated in Table 3 and Table 4) may be directed to relevant findings in the patient, but should always include an assessment of hepatomegaly and splenomegaly. Height measurement is required at screening only.

9 Eye Exam

A detailed eye history and exam must be performed at screening. The eye exam should test visual acuity, refraction, pupillary function, ocular motility, and intraocular pressure. Perform a retinal examination, particularly noting the appearance of the retinal vasculature. Describe

any signs of serious vascular occlusion (both venous and arterial) in the retina. Also, clinically evaluate for photophobia, conjunctival disease, uveitis, and cataracts. Additional exams at screening or thereafter should be performed as clinically indicated.

10 Complete Blood Count with Differential

Complete blood count (CBC) with differential is defined as peripheral blood total white blood cell (WBC) count, hemoglobin, hematocrit, platelet count, absolute neutrophil count (ANC), and WBC differential reported individually for each cell type. Cell types required for diagnosis and response assessment must be quantified including basophils, myelocytes, metamyelocytes, promyelocytes, and blasts, when present. Hematologic assessments must be obtained at screening and at every subsequent assessment, as specified in the Schedule of Events (Table 3 and Table 4) or more frequently as clinically indicated (eg, to confirm loss of hematologic response as defined in Section 16.5.1.3).

11 Serum Analysis

a) Chemistry

Serum chemistry 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), fasting glucose, albumin, creatinine, total bilirubin (direct and indirect), AST, ALT, alkaline phosphatase, magnesium, phosphorous, calcium, amylase, and lipase.

The full chemistry panel must be obtained at screening and at every subsequent assessment—with the exception of assessments on Day 15 during Cycle 2 and Cycle 3 which are lipase only— as specified in the Schedule of Events (Table 3 and Table 4) or more frequently as clinically indicated.

b) Hepatitis B Serology

At the time of screening, blood serum must be tested for Hepatitis B serology (Hepatitis B Surface Antigen, Hepatitis B Core Antibody, and Hepatitis B Surface Antibody) at minimum.

c) Fasting Cholesterol/Lipid Assessment

Fasting serum lipid panel (total, HDL, LDL) including triglycerides must be collected during screening and at subsequent time points as specified in the Schedule of Events (Table 3 and Table 4) or more frequently as clinically indicated.

d) HbA1c, CRP, Troponin, and NT-proBNP or BNP

Hemoglobin A1c (HbA1c), C-reactive protein (CRP), cardiac troponin (cTn) (either T or I is acceptable, but whichever is used must be used consistently for a given patient), and N-terminal pro-brain natriuretic peptide (NT-proBNP) or BNP must be performed at screening. Additionally, HbA1c, CRP, cTn, and NT-proBNP (or BNP) must be performed at the times specified in the Schedule of Events (Table 3 and Table 4) or more frequently as clinically indicated. If the investigative site is unable to perform NT-proBNP testing, a BNP test can be performed instead.

12 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 postmenopausal [defined as amenorrhea

for at least 12 months]) do not need to have the test performed. The test must be performed within 7 days of first dose of study drug and known to be negative prior to randomization. Women of childbearing potential at study start must also complete the pregnancy test at the End-of-Treatment visit.

13 Electrocardiogram

All ECGs must be 12-lead ECGs. The screening ECG must be performed within the 21-day screening window prior to randomization. Additionally, 12-lead ECGs must be performed in cycles 3, 6, 12, 18, every 6 cycles thereafter, and at end-of-treatment, as specified in the Schedule of Events, or more frequently if clinically indicated. If prolongation of the QTcF interval is observed ECG monitoring should be utilized as described in Section 12 and as clinically indicated.

14 Echocardiogram

An echocardiogram (ECHO) for assessment of left ventricular ejection fraction (LVEF) must be performed within the 21-day screening window and every 12 cycles and at end of treatment, as specified in the Schedule of Events. Additional ECHOs need only be performed if clinically indicated.

15 Adverse Events and Concomitant Medications

Adverse events and concomitant medications are to be recorded continuously throughout the treatment period, starting on date of signed informed consent, and at the 30-day follow-up visit, as indicated in the Schedule of Events (Table 3 and Table 4). It is expected that new and updated AEs and concomitant medications reported within the treatment period, ongoing AEs thought to be at least possibly study-drug related, and all ongoing SAEs should be followed at least every 4 weeks until they resolve to baseline (or CTCAE grade ≤1), stabilize, or are considered to be chronic or irreversible.

16 Bone Marrow Aspirate/Cytogenetics

The BM aspirate results must include the components required for assessing response of the patient. All BM aspirates must quantify cell types required for diagnosis and response assessment, including promyelocytes and blasts. Examination must include cytogenetic assessment by conventional banding. Bone marrow cytogenetics requires examination of at least 20 metaphases. If less than 20 metaphases are examined, a real time PCR with > 1% of BCR/ABL1^{IS} is required to be eligible, within the same time window.

The BM aspirate with or without an optional biopsy or real time PCR must occur within 42 days prior to randomization and ± 7 days of the subsequent scheduled assessment at cycle 12. A BM aspirate with cytogenetic assessment of 20 metaphases is required in all patients on study after the first 12 cycles, and for patients who are not in CCyR, every 12 cycles thereafter.

For patients documented to be in MCyR by the protocol definition of ≤1% BCR-ABL1^{IS}, and who have not yet undergone a post-screening BM aspirate, if ≤ 1% BCR-ABL1^{IS} is lost prior to a scheduled BM aspirate, a BM aspirate and cytogenetics must be obtained.

At the end of cycle 12, all patients must undergo a BM aspirate and cytogenetic assessment. After cycle 12, patients documented to be in CCyR after any BM aspirate and cytogenetics assessment, and also in MMR, are not required to have any further BM aspirates. As outlined

in Table 6, any patient who has greater than a 1-log (ie, 10-fold) increase in transcript level and >10-fold increase in BCR-ABL1 from nadir or BCR-ABL1 >10% should have a BM cytogenetics assessment unless the patient remains at ≤ 1% BCR-ABL1^{IS}.

A BM aspirate and cytogenetic assessment must be performed at the End-of-Treatment visit if there have been no on-treatment BM assessments or if the patient has greater than a 1-log (ie, 10-fold) increase in transcript level and >10-fold increase in BCR-ABL1 from nadir or BCR-ABL1 >10%, unless the patient remains at ≤ 1% BCR-ABL1^{IS}. BM aspirates and cytogenetic assessments may be performed at other times when clinically indicated (eg, to confirm loss of cytogenetic response as defined in Section 16.5.1.2). Results of any BM aspirate or cytogenetic assessment, whether scheduled or unscheduled, must be recorded in the patient's electronic case report form (eCRF).

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21 End-of-Treatment or Early Termination Procedures

The End-of-Treatment (or Early Termination) visit should be performed within 2 weeks (14 days) of the patient's last dose of study drug or the patient/investigator decision to discontinue treatment, whichever is later. A follow-up visit should be conducted approximately 30 days (±7 days) after the last dose of study treatment. For both visits, the information may be collected from tests that were performed for the study or as part of the patient's routine medical care. See Section 12.2.2 for further details on discontinuation of patients from study drug.

22 Follow-up Procedures: Safety

All AEs ongoing or starting within 30 days after the End-of-Treatment must be recorded on the eCRF. After this time, ongoing AEs thought to be at least possibly study-drug related and all ongoing SAEs should be followed at least every 4 weeks until they resolve to baseline (or CTCAE grade ≤1), stabilize, or are considered to be chronic or irreversible.

23 Follow-up Procedures: Survival

Survival data will be collected every 12 weeks ± 2 weeks starting after the last dose of study treatment or the investigator/patient decision to discontinue treatment, whichever occurs later. These data do not need to be obtained during a visit; phone contact is acceptable.

Table 3 Schedule of Events Through Cycle 12

Cycle	Screening/ Baseline	Cycle 1			Cycle 2		Cycle 3		Cycle 6	Cycle 9	Cycle 12
Day within Cycle	-21 to 1[1]	1	15	28	15	28	15	28	28	28	28
Informed Consent[2]	X										
Randomization (Phase 3 Only)[3]	X										
Medical/Surgical History and Demographics[4]	X										
Leukemia Diagnosis and Prior Cancer Therapy[5]	X										
BCR-ABL1 Mutation History[6]	X										
Vital Signs[7]	X	X	X	X		X		X	X	X	X
Physical Exam and ECOG Performance Status [8]	X	X	X	X		X		X	X	X	X
Eye Exam[9]	X	THROUGHOUT TREATMENT PERIOD AS CLINICALLY INDICATED									
Complete Blood Count with Differential[10]	X	X	X	X	X	X	X	X	X	X	X
Chemistry[11a]	X	X	X	X	X[a]	X	X[a]	X	X	X	X
Hepatitis B Serology[11b]	X										
Fasting Cholesterol/Lipid Assessment[11c]	X			X				X	X	X	X
HbA1c, CRP, Troponin, and NT-proBNP or BNP[11d]	X			X				X	X	X	X
Pregnancy Test [12]	X										
12-Lead Electrocardiogram [13]	X							X	X		X
Echocardiogram[14]	X										X
Adverse Events[15]	X	THROUGHOUT TREATMENT PERIOD									
Concomitant Medications[15]	X	THROUGHOUT TREATMENT PERIOD									
Bone Marrow Aspirate and Cytogenetics[16]	X										X
CCI	[redacted]										

For footnotes, see Section 12.1.
BCR-ABL1= Breakpoint Cluster Region-Abelson; CRP = C-reactive protein; ECOG = Eastern Cooperative Oncology Group; FACT-Leu = Functional Assessment of Cancer Therapy – Leukemia; HbA1c = hemoglobin A1c; NT-proBNP = N-terminal pro-brain natriuretic peptide.
a Indicates lipase only assessments.

Table 4 Schedule of Events after Cycle 12, End-of-Treatment Visit, and Survival Follow-Up

Cycle	Cycle 15	Cycle 18	Cycle 21	Cycle 24	Every 3 Cycles Thereafter	Every 6 Cycles Thereafter	Every 12 Cycles Thereafter	End-of-Treatment Visit[21]	30-Day Follow-Up Visit[21]	Survival Follow-up[23]
Day within Cycle	**28**	**28**	**28**	**28**	**28**	**28**	**28**	**N/A**	**N/A**	**N/A**
Vital Signs[7]		X		X		X		X	X	
Physical Exam and ECOG Performance Status [8]		X		X		X		X	X	
Eye Exam [9]	THROUGHOUT TREATMENT AS CLINICALLY INDICATED									
Complete Blood Count with Differential[10]		X		X		X		X	X	
Chemistry[11a]		X		X		X		X	X	
Fasting Cholesterol/Lipid Assessment[11c]		X		X		X		X		
HbA1c, CRP, Troponin, and NT-proBNP or BNP[11d]		X		X		X		X		
Pregnancy Test[12]								X		
12-Lead Electrocardiogram[13]		X		X		X		X		
Echocardiogram[14]				X			X	X		
Adverse Events [15]	THROUGHOUT TREATMENT PERIOD								X	
Concomitant Medications[15]	THROUGHOUT TREATMENT PERIOD								X	
Bone Marrow Aspirate and Cytogenetics[16]				X[15]			X[15]	X		
CCI [redacted]										
Survival[23]										X

For footnotes, see Section 12.1.
CRP = C-reactive protein; ECOG = Eastern Cooperative Oncology Group; FACT-Leu = Functional Assessment of Cancer Therapy – Leukemia; HbA1c = hemoglobin A1c; N/A = not applicable; NT-proBNP = N-terminal pro-brain natriuretic peptide.

12.2 Patient Registration and Identification

Demographic information on all patients who sign the Informed Consent Form will be recorded on the eCRF. Those patients who complete screening procedures and meet all eligibility criteria may be enrolled into the study using the enrollment procedure established by the sponsor. The patient will be assigned a unique identification code (number), consisting of a study site number and a unique consecutive number.

12.2.1 Screen Failures

Patients who have signed informed consent and subsequently fail to meet the inclusion and/or exclusion criteria are defined as screen failures. Once the Investigator determines that screening will not continue for a patient and the patient will not be enrolled in the study, the screen failure should be documented on the Eligibility Criteria eCRF within 5 days. For all screen failures, the investigator is to maintain a screening log that documents the patient's initials and reason(s) for screen failure. A copy of the log should be retained in the investigator's study files. Any patient who is re-screened after screen failure must, in addition to the failed procedure, repeat only those screening procedures outlined in the Schedule of Events (Table 3) that have fallen outside the specified screening period.

12.2.2 Early Discontinuation from Study Drug Administration or Assessments

In the event that a patient is withdrawn from the study, every effort will be made by the investigator to document and report the reason for withdrawal as thoroughly as possible. The reason for termination must be clearly reported on the appropriate page of the patient's eCRF. An End-of-Treatment reason for discontinuation must be recorded for any patient who is enrolled (phase 2) or randomized (phase 3).

If a patient is discontinued from the study for any reason, every effort must be made to perform all clinical and laboratory procedures as scheduled for the End-of-Treatment visit. 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 the End-of-Treatment eCRF.

12.3 Study Duration

The estimated duration of the phase 2 portion of the study is approximately 68 months, including 8 months for enrollment and 60 months of treatment/follow-up.

Total maximum study duration of the phase 3 portion of the study is expected to be approximately 84 months (7 years). This includes an enrollment period of approximately 24 months and a treatment period of 60 months (5 years), unless the patient is discontinued early. The duration of therapy will be determined by the patient's response and toxicity. Patients will be followed for 30 days after last dose of study drug.

The estimated duration of the study overall (both phases) is approximately 104 months, consisting of:

- Approximately 20 months for phase 2 until the primary endpoint:
  - 8 months for enrollment, and
  - 12 months for treatment/follow-up to the primary endpoint, followed by

- 84 months for phase 3 up to the end of the study:
  - 24 months for enrollment, and
  - 60 months of treatment/follow-up to the end of the study.

Patients in both phases will be followed up to 60 months as defined in the protocol after they are evaluated for the primary endpoint at 12 months; however, enrollment in phase 3 will begin after patients in phase 2 are evaluated for the primary endpoint at 12 months.

The overall study design may be modified based on the data from phase 2 that will inform the phase 3 portion of the study.

12.4 Withdrawal Criteria

Patients will be discontinued from further study drug administration if any of the following occur:

- Intolerable toxicity as determined by the investigator and defined in Section 14.4.2.1
- Myocardial infarction, unstable angina, stroke, TIA, or urgent revascularization
- A treatment interruption for study-drug related nonhematologic toxicities lasting longer than 28 days
- Absence of CHR by 3 months
- Absence of MCyR by 12 months
- For patients in the ponatinib arms, confirmed loss of MCyR in the absence of dose re-escalation (in patients unable to dose escalate due to toxicity) or continued loss of MCyR after 6 months following dose re-escalation
- For patients in the nilotinib arm, loss of MCyR
- Progression of disease to AP- or BP-CML
- Entry into another therapeutic clinical study 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 study by the sponsor
- Any other reason that, in the opinion of the investigator, would justify removal of the patient from the study

Please ensure that patients discontinuing treatment or assessments early have adequate follow up as described in Section 12.1.

12.5 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 participation should be terminated, this action may be taken after appropriate consultation between the sponsor and the investigator.

Conditions that may warrant termination of the study include, but are not limited to:

- The discovery of a serious, unexpected, or unacceptable risk to patients enrolled in the study
- The decision on the part of the sponsor to suspend or discontinue testing, evaluation, or development of the study treatment
- Submission of knowingly false information from the research facility to the sponsor, medical monitor, or regulatory authorities
- Insufficient adherence to protocol requirements

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

Criteria for removing individual patients from the study are outlined in Section 12.4.

12.6 Sample Collection, Storage, and Shipping

Specific instructions for sample collection, storage, and shipping are included in the Study Reference Manual.

13 EFFICACY AND SAFETY ASSESSMENTS (PHASE 2 AND PHASE 3)

The following sections describe the procedures/tests required for this study.

13.1 Efficacy Assessments

Efficacy assessments are described in Section 12.1 and comprise:

- BCR-ABL1 transcript assessment to determine molecular response
- Bone marrow aspirates for assessment of cytogenetic response
- Complete blood count for assessment of hematologic response
- Survival follow-up

13.2 Safety Assessments

Safety will be assessed by routine physical and laboratory evaluations, ECGs, and ECHOs, and AEs will be recorded and the severity will be graded according to the NCI CTCAE v.4.0 (see Appendix C and Study Reference Manual).

13.2.1 Adverse Events

AE type, incidence, severity (graded in accordance with the NCI CTCAE v.4.0), timing, seriousness and relatedness, outcome, action taken with study drug, and treatment will be assessed and documented by the investigator continuously throughout the study.

Baseline CML-related signs and symptoms will be recorded as AEs during the study if they worsen in severity or increase in frequency.

The number and percentages of patients who developed AOEs and VTEs will be summarized for each cohort as described in Section 16.6.1.

13.3 Exploratory Biomarker Evaluations in Tissue and Plasma

CCI

[redacted]

13.4 Quality of Life Assessments

CCI

[redacted]

14 STUDY TREATMENT

14.1 Study Treatment

For the phase 2 portion, all patients will receive ponatinib 15 mg once daily (QD). As described in Section 14.2, patients will have their daily dose of ponatinib reduced to 10 mg if MMR has been achieved.

For the phase 3 portion, the starting dose of study drug will be 30 mg ponatinib QD (Cohort A), 15 mg ponatinib QD (Cohort B), or 400 mg nilotinib BID (Cohort C), taken orally. Study drug will be self-administered by the patient on a daily schedule. As described in Section 14.2, patients in Cohort A will have their daily dose of ponatinib reduced to 15 mg and patients in Cohort B will have their daily dose of ponatinib reduced to 10 mg if MMR has been achieved.

Study treatment will be administered only to eligible (and, for the phase 3 portion, randomized) patients at qualified centers (eg, listed on the FDA Form 1572).

14.1.1 Treatment Administration

Patients in the phase 2 portion and in Cohorts A and B of the phase 3 portion will take the prescribed number of ponatinib tablets with water, with or without food, at approximately the same time each day. Patients in Cohort C will take the prescribed number of nilotinib capsules approximately 12 hours apart at approximately the same time each day. Nilotinib capsules should be swallowed with water and must not be taken with food. Patients should not consume food 2 hours before or 1 hour after the dose of nilotinib is taken. Patients in all cohorts will be provided a diary card or equivalent where the date and time of administration will be recorded; complete instructions will be provided with the Study Reference Manual. Patients who forget to take their dose more than 6 hours after it is due should not make up the missed dose. Any missing doses should be recorded, and subsequent training of patients should be documented in the appropriate source record (eg, clinic chart) and in the eCRF.

14.2 Ponatinib Treatment for Patients in Phase2 and Cohorts A and B in Phase 3

The starting dose of study drug will be 15 mg ponatinib QD (phase 2), 30 mg ponatinib QD (Cohort A of phase 3), 15 mg ponatinib QD (Cohort B of phase 3). Each 28-day dosing period is referred to as 1 cycle. Patients will be assessed for MMR and MCyR as described below, and doses will be modified according to response. Doses may also be modified to manage AEs, also described below.

14.2.1 Mandatory Dose Reduction for Response Scheme in Phase 2 and Ponatinib Cohorts A and B in Phase 3

Patients will be assessed for molecular and cytogenetic response at 3-month intervals. Patients in the ponatinib cohorts will have their doses reduced upon attainment of MMR at 3, 6, 9, or 12 months or MCyR at 12 months, as defined below and in Sections 16.5.1.1 and 16.5.1.2. No dose reduction for response will be implemented for patients in the nilotinib cohort. The dose reduction scheme is described in Table 5.

MMR is defined as a ≤0.1% ratio of BCR-ABL1 to ABL1 transcripts on the IS (BCR-ABL1^{IS}), measured by real-time quantitative PCR.

MCyR is defined according to standard criteria as ≤35% Ph+-containing metaphases (typically ≤7/20 involved metaphases), that is, as either a PCyR or a CCyR. Increasingly, patient monitoring is being performed by quantitation of BCR-ABL1 transcript from a standard according to the international scale (IS) (Marin, 2014; Baccarani et al, 2013; Marin et al, 2012; Lauseker et al, 2012; Saglio et al, 2012). This is in fact the recommendation of the National Comprehensive Cancer Network (NCCN; O'Brien et al, 2014). Using such monitoring, ≤1% BCR-ABL1/ABL1^{IS} is taken to be equivalent to CCyR (Marin, 2014).

Patients will undergo a baseline BM aspirate and cytogenetics to establish the diagnosis and eligibility. They will then undergo molecular monitoring at 3-month intervals (or when an unscheduled assessment is performed) for the assessment of response. In the ponatinib arms (phase 2 and Cohorts A and B of phase 3), the assessment will also inform the decision regarding dose reduction. They will undergo a BM aspirate with cytogenetics after 12 cycles, which will be used to assess cytogenetic response at 12 months and to inform the decision regarding dose reduction, at end of treatment as specified in the Schedule of Events (Table 4), and other time points depending on response. Details of BM acquisition are also listed in Section 12.1, item 15.

Note: patients may undergo dose reduction for adverse events (see Section 14.3) prior to the achievement of MMR. This should not affect the assessment of response and the mandated dose reduction in patients enrolled in the ponatinib cohorts upon its attainment.

The schedule of patient assessment for mandatory response-related dose reduction in phase 2 and Cohorts A and B in phase 3 is as follows:

At 3 months, patients in Cohorts A and B will have their dose reduced to 15 mg and 10 mg, respectively, if they are in MMR; if not, they will continue at their current dose until the 6-month assessment.

At 6 months, patients in Cohorts A and B will have their dose reduced to 15 mg and 10 mg, respectively if they are in MMR. If not, they will continue at their current dose until the 9-month assessment.

At 9 months, patients in Cohorts A and B will have their dose reduced to 15 mg and 10 mg, respectively, if they are in MMR. If not, they will continue at their current dose until the 12-month assessment.

At 12 months, all patients will undergo a BM aspirate and cytogenetics. Patients in phase 2 will have their dose reduced to 10 mg and patients in Cohorts A and B of phase 3 will have their dose reduced to 15 mg and 10 mg, respectively, if they are in MMR, and will continue therapy.

At 12 months, dose reduction upon achieving an MCyR may occur following discussion with the Medical Monitor. If not in MCyR at 12 months, patients will discontinue therapy.

Ponatinib dose reduction upon achievement of MMR can also be implemented when an unscheduled response assessment is performed.

Table 5 Mandatory Study Drug Dose Modifications Based on Response[a]

Response Criteria	Time Point	Value	Cohort	Action
MMR (≤0.1%)	3 months and every subsequent 3 months or when an unscheduled response assessment is performed	MMR	Phase 2	Reduce dose to 10 mg
			Phase 3	
			A	Reduce dose to 15 mg
			B	Reduce dose to 10 mg
			C	No change in dose
MCyR by BM cytogenetics (upon discussion with Medical Monitor)	12 months	MCyR	Phase 2	Reduce dose to 10 mg
			Phase 3	
			A	Reduce dose to 15 mg
			B	Reduce dose to 10 mg
			C	No change in dose
		Not in MCyR	All	Discontinue from study

a Once a patient re-escalates due to loss of response, that patient should not be dose-reduced again upon re-achievement of MMR or MCyR by BM cytogenetics

Refer to Section 12.4 for additional criteria for discontinuation for patients not achieving response.

14.2.2 Loss of Response after Dose Reduction for MMR or MCyR in Phase 2 and in Cohorts A and B of Phase 3

Patients being treated with ponatinib who achieve MMR at any time point, undergo dose reduction, and then lose MMR, as determined by real-time quantitative PCR assessment (Section 16.5.1.1), are candidates for dose re-escalation to their starting dose, in the absence of AEs requiring dose modification. Patients who achieve MCyR, but not MMR, at 12 months also will undergo dose reduction. These patients who subsequently lose MCyR are also candidates for dose escalation at the discretion of the physician.

Patients will be monitored with a cytogenetic assessment at 12 months and molecular response assessments every 3 months according to the Schedule of Events (Table 3 and Table 4, or in the case of an unscheduled assessment). Any patient who has a greater than 1-log increase in transcript level should also have a BM cytogenetic assessment performed unless the patient remains at ≤ 1% BCR-ABL1^{IS}. If the cytogenetic assessment indicates loss of MCyR, dose escalation may be considered. If the cytogenetic assessment does not demonstrate loss of MCyR, continued monitoring is indicated.

Patients may be dose re-escalated as follows:

Patients may only undergo dose re-escalation if they do not have ongoing AEs necessitating treatment at 10 mg or 15 mg as per Section 14.4.2 (Dose Modifications for Adverse Drug Reactions).

For patients in Cohort A of phase 3, re-escalate to the starting dose of 30 mg. For patients in phase 2 and Cohort B of phase 3, escalate to the starting dose of 15 mg.

If patients regain MCyR after dose escalation, continue their therapy at the escalated dose and monitor according to the Schedule of Events (Table 3 and Table 4).

If patients do not regain MCyR after 6 months of therapy at the escalated dose, they must be discontinued from the study.

The dose re-escalation scheme is described in Table 6.

Table 6 Ponatinib Dose Re-escalation Following Loss of Response After Dose Reduction

Current Response Criteria	Time Point	Cohort	Action
Loss of MCyR by cytogenetics	12 months or later	Phase 2	Re-escalate to 15 mg[a]
		Phase 3	
		A	Re-escalate to 30 mg[a]
		B	Re-escalate to 15 mg[a]
If • Loss of ≤ 1% BCR-ABL1^{IS} (ie, ≥1% BCR-ABL1) and >10-fold ↑in BCR-ABL1 from nadir	Any time after achievement of MCyR or MMR	Phase 2	Perform BM cytogenetics; if loss of MCyR then re-escalate to 15 mg[a]; if no loss of MCyR, continue to monitor according to SOE
		Phase 3	

or • BCR-ABL1 >10%		A	Perform BM cytogenetics; if loss of MCyR then re-escalate to 30 mg[a]; if no loss of MCyR, continue to monitor according to SOE
		B	Perform BM cytogenetics; if loss of MCyR then re-escalate to 15 mg[a]; if no loss of MCyR, continue to monitor according to SOE

a unless dose-reduction was due to AEs

14.3 Nilotinib Treatment for Patients in Cohorts C

The starting dose of study drug will be 400 mg nilotinib BID (Cohort C). Each 28-day dosing period is referred to as 1 cycle. Patients will be assessed for MMR and MCyR as described above, but in contrast to the ponatinib arms, doses will not be modified according to achievement of response. Doses may be modified to manage AEs, as described below.

14.4 Adverse Event Management

An analysis of baseline risk factors in patients from the phase 2 PACE study assessed the impact of hypertension, hypercholesterolemia, diabetes, and obesity, and revealed several risk factors that predispose patients to AOEs and VTEs on ponatinib. Based on this analysis, the leading risk factors for serious AOEs and VTEs are cardiovascular disorders such as any history of myocardial infarction, coronary artery disease, coronary revascularization, and history of ischemic cerebrovascular disease, diabetes mellitus, hypertension, and hypercholesterolemia. The following supportive care recommendations are provided to address these conditions and the risk of AOEs and VTEs for patients taking ponatinib.

Nilotinib also is associated with AOEs. Less is known about the contribution of risk factors to nilotinib-associated AOEs but the literature suggests that similar risk factors contribute to these events in the course of nilotinib therapy (Valent et al, 2015).

The following supportive care recommendations are provided to address these conditions and the risk of AOEs and VTEs for patients taking ponatinib and the risk of AOEs for patients taking nilotinib. At this time, there are no data that demonstrate that these recommendations are effective in lessening the risk of AOEs and VTEs but they constitute standard care for patients with these contributing conditions.

Antidiabetic Treatment

Patients with diabetes are at increased risk of experiencing arterial occlusive events while being treated with ponatinib. Therefore, as a part of the assessment and management of the patient's cardiovascular risk factors, initiation of or modifications to diabetic care should be considered in patients who have elevated glucose levels. The American Diabetes Association guidelines should be followed, and diabetic treatment and lifestyle intervention (including but not limited to weight loss, decreased fat intake, calorie restriction, increased physical activity, and smoking cessation) should be started in any patient with fasting glucose >130 mg/dL (7.2 mmol/L) and/or HbA1c ≥7% (Diabetes Prevention Program Research Group, 2002; American Diabetes Association, Position Statement 2013).

Hypertension Treatment

Hypertension (HTN) may contribute to the risk of arterial occlusive events. Patients who have HTN should be managed appropriately before initiating treatment. During study treatment, blood pressure elevations should be monitored and elevations managed. Hypertension should be treated to achieve a goal of <150/90 mmHg. Initial antihypertensive treatment should generally include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB) (James et al, 2014). Specific management of an individual patient should be determined by the treating physician. Study treatment should be temporarily interrupted if HTN is not medically controlled (refer to Section 14.4.1.1.5 below for additional management recommendations). Patients may require urgent clinical intervention for HTN associated with confusion, headache, chest pain, or shortness of breath.

14.4.1 Management of Selected Adverse Events

Dose reduction guidelines are outlined in Section 14.4.2.1. This section provides additional guidance for management of selected AEs for both ponatinib and nilotinib.

Comprehensive assessments of any study drug-related AEs (adverse drug reactions) experienced by the patient will be performed throughout the course of the study. Adverse drug reactions that may be experienced are described in the current Investigator's Brochure for ponatinib and the current SmPC for Tasigna (Nilotinib SmPC, 2016) for nilotinib. The severity of the event, as well as clinical judgment, will be utilized to determine appropriate management of the patient for any AE experienced while participating in this study.

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

The current SmPC for Tasigna (nilotinib) should be used as the reference safety information for the nilotinib drug.

14.4.1.1 Adverse Events Common to Ponatinib and Nilotinib

14.4.1.1.1 Arterial Occlusive and Venous Thrombotic/Embolic Events

Serious arterial and venous thrombotic and occlusive AEs, including fatal MI, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures have occurred in ponatinib-treated patients. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. AOEs were more frequent with increasing age and in patients with prior history of ischemia, hypertension, diabetes, or hyperlipidemia.

Similar events have been observed in nilotinib-treated patients.

Arterial Occlusion

Serious arterial occlusive AEs occurred in ponatinib-treated patients; some patients experienced events of more than one type. Serious cardiovascular occlusive AEs included MI and coronary artery disease. Some patients developed CHF concurrent or subsequent to the myocardial ischemic event.

Serious cerebrovascular occlusive AEs were also reported in ponatinib-treated patients. Some patients developed stenosis of large arterial vessels of the brain (eg, carotid, vertebral, or middle cerebral artery).

Serious peripheral arterial occlusive AEs were reported in ponatinib-treated patients; some developed digital or distal extremity necrosis with complications of diabetes mellitus and peripheral arterial disease that required amputations.

Similar events occur in nilotinib-treated patients. Ischemic cardiac AEs, peripheral arterial occlusive disease, and cerebral arterial events were observed in newly diagnosed patients.

Monitor and aggressively treat factors that increase cardiovascular risk, such as hypertension, smoking, hypercholesterolemia, and hyperglycemia. Interrupt and consider discontinuation of study drug in patients who develop arterial occlusive AEs. Any patient who experiences a serious adverse event of MI, unstable angina, stroke, or urgent revascularization while on study must be discontinued from the study unless the investigator believes that the potential benefits of ponatinib or nilotinib treatment are likely to exceed the risks of continued treatment for that individual patient and the patient has no other treatment options.

Venous Thromboembolism

Serious venous thromboembolic AEs occurred in ponatinib- and nilotinib-treated patients, including deep venous thrombosis, pulmonary embolism, superficial thrombophlebitis, and retinal vein thrombosis. Consider dose modification or discontinuation of treatment in patients who develop serious venous thromboembolic AEs. Neither ponatinib nor nilotinib should be restarted in patients with serious venous occlusive AEs unless the investigator believes that the potential benefit outweighs the risk of recurrent venous occlusions and the patient has no other treatment options.

14.4.1.1.2 Electrolyte abnormalities

Both ponatinib and nilotinib can cause hypophosphatemia, hypokalemia, hyperkalemia, hypocalcemia, and hyponatremia. These should be monitored periodically and corrected during therapy.

14.4.1.1.3 Neuropathy

Serious peripheral and cranial neuropathic AEs have occurred in ponatinib-treated patients. In clinical studies, serious peripheral neuropathic AEs reported included peripheral neuropathy, paresthesia, hypoesthesia, and hyperesthesia. Of the patients who developed neuropathy, many did so during the first month of treatment. Peripheral neuropathy is also reported as a common adverse reaction for nilotinib. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness. Consider interrupting study treatment and evaluate if neuropathy is suspected.

14.4.1.1.4 Hepatotoxicity

Hepatotoxicity, most commonly manifested by reversible transaminase and alkaline phosphatase elevation and hyperbilirubinemia, has been observed with ponatinib. Elevations of transaminases, alkaline phosphatase, and bilirubin have also been associated with nilotinib.

Monitoring of hepatic function is recommended, and laboratory abnormalities should be managed with dose interruption and/or dose reduction according to Table 7 and Table 8.

14.4.1.1.5 Hypertension

Hypertension is associated with both ponatinib and nilotinib therapy. Blood pressure should be monitored at each visit. Hypertension (HTN) detected by at least 2 blood pressure measurements should be graded according to NCI CTCAE version 4.0, which defines HTN as a disorder characterized by a pathological increase in blood pressure, a repeated elevation in the blood pressure exceeding 140 mmHg for systolic and over 90 mmHg for diastolic. Aggressive antihypertensive medication should be initiated or optimized to achieve target blood pressure for patients who either develop HTN or experience worsening HTN during study treatment before interruption or dose reduction of the study treatment. If hypertension is persistent despite aggressive antihypertensive therapy (i.e., 3 or more medications), or if grade 3 or 4 HTN develops, dose interruption and reduction is recommended according to Dose Modification Guidelines for general nonhematologic AEs in Table 7 and Table 8.

14.4.1.1.6 Pancreatitis and Lipase or Amylase Elevations

Pancreatitis (symptomatic abdominal pain associated with pancreatic enzyme elevation) and/or elevations in lipase and amylase are known AEs associated with ponatinib and nilotinib. Most cases of pancreatitis or elevated pancreatic enzymes occur within the first 2 months of treatment. These events are generally uncomplicated and reversible and can be managed with both a brief interruption of treatment and standard medical therapies. Almost all patients are able to continue on with ponatinib treatment at either the same or a reduced dose once the event has improved to grade 1 or resolved. Patients with low-grade (NCI CTCAE version 4.0 grade 1 or 2) elevation in amylase can be continued without dose reduction but should be monitored closely with serial enzyme level determinations. See Table 7 for details.

14.4.1.1.7 Hemorrhage

Hemorrhagic events have occurred in patients receiving ponatinib. Most of these events occurred in patients with grade 4 thrombocytopenia. Hemorrhagic events, including gastrointestinal and CNS hemorrhage, have also been reported in studies of nilotinib. Interrupt administration in case of serious or severe hemorrhage.

14.4.1.1.8 Fluid Retention and Edema

Both ponatinib and nilotinib are associated with edema and occasionally serious fluid retention. Patients should be weighed and monitored regularly for signs and symptoms of fluid retention. An unexpected and rapid weight gain should be carefully investigated and appropriate treatment provided. Interrupt, reduce the dose of, or discontinue therapy as outlined in Table 7 and Table 8.

14.4.1.1.9 Cardiac Arrhythmias

Supraventricular tachyarrhythmias have been reported in patients treated with ponatinib or nilotinib. Advise patients to report signs and symptoms of rapid heart rate (such as palpitations or dizziness). Symptomatic bradyarrhythmias have also been reported. Advise patients to report signs and symptoms suggestive of slow heart rate (including fainting, dizziness, or chest pain, see Table 7 and Table 8).

14.4.1.1.10 Myelosuppression

Neutropenia, anemia, and thrombocytopenia have been observed in clinical studies of ponatinib and nilotinib in patients with CML. While myelosuppression can occur any time during treatment, its onset in CML patients most commonly occurs within the first month of treatment. Myelosuppression can partially be attributed to the CML itself; however, treatment with ponatinib could also contribute. These events can typically be managed with supportive care and, if believed by the investigator to be treatment-related, either a reduction or interruption of treatment with ponatinib or nilotinib should occur (Table 7 and Table 8). Rarely, one or more cytopenias can lead to permanent discontinuation of treatment. The use of hematopoietic growth factors such as granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor is permitted on study; these agents may be used to support blood counts as clinically indicated to minimize treatment interruptions or repeated dose reductions.

The important clinical AE of febrile neutropenia falls under the broad category of myelosuppression. If a patient's individual risk factors present a high risk of developing febrile neutropenia, primary prophylactic use of colony-stimulating growth factors for the prevention or reduction of febrile neutropenia is recommended according to the published NCCN guidelines (NCCN Guidelines Version 1.2012 – Myeloid Growth Factors).

14.4.1.1.11 Tumor Lysis Syndrome (TLS)

Tumor lysis syndrome occurs in patients treated with both ponatinib and nilotinib. The patients at risk of TLS are those with high tumor/leukemic burden prior to treatment. These patients should be monitored closely, especially at the initiation of treatment. Appropriate TLS precautions and prophylactic treatment (such as aggressive hydration with fluids and the initiation of allopurinol at 600 mg/day or other appropriate treatments) should be initiated prior to the start of therapy for those deemed at risk. Rasburicase and other appropriate treatments for hyperuricemia or TLS are permitted.

14.4.1.1.12 Rash and/or Pruritus

Skin rashes have been commonly reported to be associated with both ponatinib and nilotinib. The vast majority of these skin events are nonserious, either self-limiting or manageable with antihistamines or topical steroids, and do not result in discontinuation. In more severe cases, a short course of oral corticosteroids may be used until the rash has improved or resolved.

In patients treated with ponatinib, the most common skin manifestations are a diffuse maculo-papular rash that is nonpruritic and an acneiform dermatitis. Occasionally, patients treated with ponatinib have been reported to have a dry, flaky, or exfoliative type of rash or a psoriasiform dermatitis. Rarely, an erythema multiforme type of rash has been associated with ponatinib.

Most patients can be maintained on their current dose of ponatinib or nilotinib, uninterrupted; if necessary, their symptoms can be managed with antihistamines, emollients, or topical steroids. If dose interruption is indicated, patients can resume the same dose typically without recurrence of symptoms once the original episode has improved or resolved. Interrupt administration in the case of serious or severe (grade 3 or 4) rash and follow the dose modification guidelines for nonhematologic toxicity in Table 7.

14.4.1.1.13 Diarrhea, Nausea, and Vomiting

Diarrhea is a common side effect of both ponatinib and nilotinib, and the use of antidiarrheal medications is permitted. Patients who experience ≥ grade 2 diarrhea may begin loperamide at its standard treatment schedule (4 mg orally × 1, than 2 mg orally after each loose stool, up to a maximum of 16 mg/day).

Nausea and vomiting are also reported as side effects of both ponatinib and nilotinib. The use of an antiemetic prophylactically is not recommended. However, if a patient is symptomatic, appropriate antiemetic medications may be used as clinically indicated.

14.4.1.1.14 Constitutional Symptoms/Joint Pain

Certain constitutional symptoms such as myalgia, arthralgia, headache, weakness, fatigue, asthenia, and low-grade fever have been commonly reported with both ponatinib and nilotinib. In studies of ponatinib, these symptoms were reported mainly at the initiation of treatment, were typically short lived (<2 weeks), and were seldom, if ever, reported beyond the first month of treatment. These AEs are most commonly low grade (grade 1 and 2) and are self-resolving without the need for dose interruption or dose reduction when they do occur. Most patients can be maintained on the current dose of ponatinib or nilotinib, uninterrupted, and their symptoms can be managed with a short course of oral analagesics, corticosteroids, and/or anti-pyretics as clinically indicated. If dose interruption is indicated, patients can resume the same dose of ponatinib or nilotinib, typically without recurrence of symptoms, once the original episode has improved or resolved.

14.4.1.2 Ponatinib-Specific Adverse Events

14.4.1.2.1 Congestive Heart Failure and Left Ventricular Dysfunction

Severe congestive heart failure (CHF) and left ventricular (LV) dysfunction have been reported in patients taking ponatinib. Patients with cardiac disease or risk factors for cardiac disease should be monitored carefully and any patient with signs or symptoms consistent with cardiac failure should be evaluated and treated. Consider discontinuation of therapy in patients who develop serious CHF.

14.4.1.2.2 Ocular Toxicity

Serious ocular adverse event toxicities leading to blindness or blurred vision have occurred in ponatinib-treated patients. Retinal toxicities including macular edema, retinal vein occlusion, and retinal hemorrhage have also occurred in ponatinib-treated patients. Other ocular toxicities include cataracts, glaucoma, iritis, iridocyclitis, and ulcerative keratitis. If decreased vision or blurred vision occurs, an ophthalmic examination (including fundoscopy) should be performed and ponatinib should be interrupted if arterial occlusive events or venous thrombotic/embolic events are suspected.

14.4.1.2.3 Compromised Wound Healing and Gastrointestinal Perforation

Ponatinib may compromise wound healing. Interrupt ponatinib for at least 1 week prior to major surgery. The decision of when to resume ponatinib after surgery should be based on clinical judgment of adequate wound healing.

14.4.1.3 Nilotinib-Specific Adverse Events

14.4.1.3.1 QT Prolongation

Nilotinib prolongs the QT interval, which can lead to arrhythmia and sudden death. Patients with prolonged QT interval at baseline are excluded from this study, as are those with uncorrected electrolyte imbalances such as hypokalemia or hypomagnesemia (which also prolong the QT interval). The use of concomitant medicines that prolong the QT interval is prohibited. Patients on study will undergo periodic ECG monitoring.

14.4.1.3.2 Sudden Death

Sudden deaths have been reported in patients receiving nilotinib. As noted above, patients with prolonged QT or with electrolyte abnormalities, which may be risk factors for sudden death, are excluded from the study.

14.4.2 Dose Modifications for Adverse Drug Reactions

14.4.2.1 Dose Reduction Guidelines for Adverse Events

Dose reduction guidelines for ponatinib are summarized in Table 7, and for nilotinib in Table 8. AEs should be graded according to NCI CTCAE v4.0. These guidelines should be followed by clinical investigators; however, for an individual patient, dose interruptions, reductions, and treatment discontinuation should also be based on the clinical circumstance. Deviation from these guidelines must be documented and communicated with the sponsor. When the observed toxicity has resolved to ≤ grade 1 or returned to baseline, the investigator may resume dosing if clinically indicated. Guidance for re-escalation after resolution of adverse drug reactions is provided in Section 14.4.2.3.

Ponatinib dose reduction below 10 mg once daily is not permitted (see Table 7). Nilotinib dose reduction below 400 mg once daily is not permitted. Doses may be interrupted for study-drug related toxicities for up to 28 days. If a nonhematologic study drug-related toxicity does not resolve to ≤ grade 1 or has not returned to baseline after dose interruption for more than 28 days, the patient must be discontinued from study treatment. If a hematologic study-drug related toxicity does not resolve to ≤ grade 1 or has not returned to baseline after dose interruption for more than 28 days, the sponsor's medical monitor must be contacted. Additionally, the sponsor's medical monitor must be contacted if any AE deemed unrelated to treatment requires dose interruption for more than 28 days.

During dose interruptions, continue to observe the study schedule as planned (Table 3 and Table 4).

Once adverse drug reactions have resolved when the guidelines below are followed, investigators are encouraged to re-escalate the dose of study drug (Section 14.4.2.3).

Table 7 Dose Modifications for Adverse Drug Reactions for Patients on Ponatinib

Toxicity	Modification
Nonhematologic Toxicity	
General	
Grade 1 or transient grade 2	No intervention
Grade 2 lasting ≥ 7 days with optimal care	First occurrence[a] at any dose level: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level Recurrence[b] at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Recurrence[b] at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Recurrence[b] at 10 mg: Discontinue ponatinib
Grade 3 or 4	Occurrence[a] at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Occurrence[a] at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Occurrence[a] at 10 mg: Discontinue ponatinib
Pancreatitis and Elevation of Lipase	
Asymptomatic grade 1 or 2 elevation of serum lipase	Consider interruption or dose reduction of ponatinib
Asymptomatic grade 3 or 4 elevation of lipase (>2 × ULN) or asymptomatic radiologic pancreatitis (grade 2 pancreatitis)	Occurrence[a] at 30 mg: Hold until event is ≤ grade 1 (≤ 1.5 x ULN), or has returned to baseline Resume at 15 mg Occurrence[a] at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Occurrence[a] at 10 mg: Discontinue ponatinib
Symptomatic grade 3 pancreatitis (severe pain, vomiting, medical intervention indicated [eg, analgesia, nutritional support])	Occurrence[a] at 30 mg: Hold until complete resolution of symptoms and after recovery of lipase elevation to ≤ grade 1 Resume at 15 mg Occurrence[a] at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Occurrence[a] at 10 mg: Discontinue ponatinib
Grade 4 pancreatitis	Discontinue ponatinib

Toxicity	Modification
Hepatic Toxicity	
Elevation of liver transaminase >3 × ULN (grade 2 or higher)	Occurrence[a] at 30 mg: Hold ponatinib and monitor hepatic function until event is ≤ grade 1 (≤ 3 ×ULN), or has returned to baseline Resume at 15 mg Occurrence[a] at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Occurrence[a] at 10 mg: Discontinue ponatinib
Elevation of AST or ALT ≥ 3 × ULN concurrent with an elevation of bilirubin >2 × ULN and alkaline phosphatase < 2 × ULN	Discontinue ponatinib
LVEF/CHF[c]	
Grade 1	No dose adjustment
Grade 2	Monitor by ECHO First occurrence[a] at any dose level: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level Recurrence[b] at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Recurrence[b] at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Recurrence[b] at 10 mg: Discontinue ponatinib
Grade 3	Monitor by ECHO Occurrence[a] at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Occurrence[a] at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Occurrence[a] at 10 mg: Discontinue ponatinib
Grade 4	Discontinue ponatinib

Toxicity	Modification
Skin rash	
Grade 1	No intervention
Grade 2 persistent despite optimal symptomatic therapy	First occurrence[a] at any dose level: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level Recurrence[b] at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Recurrence[b] at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Recurrence[b] at 10 mg: Discontinue ponatinib
Grade 3 persistent despite optimal symptomatic therapy	First occurrence[a] at any dose level: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level Recurrence[b] at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Recurrence[b] at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Recurrence[b] at 10 mg: Discontinue ponatinib
Hematologic Toxicity	
***Drug-Related* ANC/platelets**	
Grade 1 or 2	No dose adjustment
Grade 3 or 4	First occurrence[a] at any dose level: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level Recurrence[b] at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Recurrence[b] at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Recurrence[b] at 10 mg: Discontinue ponatinib

ANC = absolute neutrophil count; CHF = congestive heart failure; CT = computed tomography; LVEF = left ventricular ejection fraction.

a "Occurrence" means the first time an AE is encountered by a patient at a given dose level.

b "Recurrence" means the second time an AE is encountered by a patient at a given dose level.

c Note: CTCAE criteria should be used to interrupt or discontinue study drug for grade 2, 3, or 4 events considered to be study drug related.
For grade 2: LVEF <50% - 40%, grade 3: LVEF <39 - 20%, grade 4: refractory CHF or LVEF <20%.

Dose modifications for patients being treated with nilotinib are below in Table 8.

Table 8 Modifications for Adverse Drug Reactions in Patients on Nilotinib

Toxicity	Modification
Nonhematologic Toxicity	
General	
Grade 1 or transient grade 2	No intervention
Grade 2 lasting ≥ 7 days with optimal care	First occurrence[a] at 400 mg BID: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level Recurrence[b] at 400 mg BID: Hold until event is ≤ grade 1, or has returned to baseline Resume at 400 mg QD Recurrence[b] at 400 mg QD: Discontinue nilotinib
Grade 3 or 4	Occurrence[a] at 400 mg BID: Hold until event is ≤ grade 1, or has returned to baseline Resume at 400 mg QD Occurrence[a] at 400 mg QD: Discontinue nilotinib
Pancreatitis and Elevation of Lipase	
Asymptomatic grade 1 or 2 elevation of serum amylase or lipase	Consider interruption or dose reduction of nilotinib
Asymptomatic grade 3 or 4 elevation of amylase or lipase (>2 × ULN)	Occurrence[a] at 400 mg BID Hold therapy and perform abdominal CT with contrast If positive for pancreatic pathology, continue to hold therapy and repeat at investigator's discretion If CT is negative, Hold until event is ≤ grade 1 (≤ 1.5 x ULN), or has returned to baseline Resume at 400 mg QD Recurrence[b] at 400 mg QD: Discontinue nilotinib
Grade 2 or 3 pancreatitis	Occurrence[a] at 400 mg BID Hold therapy and perform abdominal CT with contrast If positive for pancreatic pathology, continue to hold therapy and repeat at investigator's discretion If CT is negative, Hold until event is ≤ grade 1 (≤ 1.5 x ULN), or has returned to baseline Resume at 400 mg QD Recurrence[b] at 400 mg QD: Discontinue nilotinib
Grade 4 pancreatitis	Discontinue nilotinib

Toxicity	Modification
Hypophosphatemia	
Grade 2	Continue 400 mg BID and start phosphate supplementation
Grade 3 or 4	First occurrence[a] at 400 mg BID: Hold, start phosphate supplementation until event is ≤ grade 2, or has returned to baseline Resume at current dose level Recurrence[b] at 400 mg BID: Hold until event is ≤ grade 2, or has returned to baseline Resume at 400 mg QD Recurrence[b] at 400 mg QD: Discontinue nilotinib
Serum creatinine	
Grade 2	First occurrence[a] at 400 mg BID: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level Recurrence[b] at 400 mg BID: Hold until event is ≤ grade 1, or has returned to baseline Resume at 400 mg QD Recurrence[b] at 400 mg QD: Discontinue nilotinib
Grade 3 or 4	First occurrence[a] at 400 mg BID: Hold until event is ≤ grade 1, or has returned to baseline Resume at 400 mg QD Recurrence[b] at 400 mg QD: Discontinue nilotinib
Hepatic toxicity (rule out hemolysis or Gilbert's syndrome)	
Grade 2 elevation of bilirubin or hepatic transaminases (AST and/or ALT)	First occurrence[a] at 400 mg BID: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level Recurrence[b] at 400 mg BID: Hold until event is ≤ grade 1, or has returned to baseline Resume at 400 mg QD Recurrence[b] at 400 mg QD: Discontinue nilotinib
Grade 3 or 4 elevation of bilirubin or hepatic transaminases (AST and/or ALT)	First occurrence[a] at 400 mg BID: Hold until event is ≤ grade 1, or has returned to baseline Resume at 400 mg QD Recurrence[b] at 400 mg QD: Discontinue nilotinib

Toxicity	Modification
Diarrhea Institute symptomatic therapy	
Grade 3 or 4	First occurrence[a] at 400 mg BID: Hold until event is ≤ grade 1, or has returned to baseline Resume at 400 mg QD Recurrence[b] at 400 mg QD: Discontinue nilotinib
Vomiting Institute symptomatic therapy	
Grade 3 or 4	First occurrence[a] at 400 mg BID: Hold until event is ≤ grade 1, or has returned to baseline Resume at 400 mg QD Recurrence[b] at 400 mg QD: Discontinue nilotinib
Skin Rash Institute symptomatic therapy	
Grade 2	First occurrence[a] at 400 mg BID: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level Recurrence[b] at 400 mg BID: Hold until event is ≤ grade 1, or has returned to baseline Resume at 400 mg QD Recurrence[b] at 400 mg QD: Discontinue nilotinib
Grade 3 or 4	First occurrence[a] at 400 mg BID: Hold until event is ≤ grade 1, or has returned to baseline Resume at 400 mg QD Recurrence[b] at 400 mg QD: Discontinue nilotinib

Toxicity	Modification
QT prolongation QTcF > 480 ms	Hold nilotinib and correct any abnormalities of serum potassium and magnesium Verify concomitant medications do not include medicines that prolong the QT interval or that are strong inhibitors of CYP3A4. If a cause for QT prolongation is identified and corrected and QTcF returns to <450 ms and to within 20 msec of screening within 2 weeks, 400 mg BID may be resumed and a repeat ECG must be performed 7 days following the dose adjustment. If QTcF is between 450 msec and 480 msec after 2 weeks, reduce to dose of nilotinib to 400 mg QD and a repeat ECG must be performed 7 days following the dose reduction. If no cause is identified and QTcF returns to <450 ms within 2 weeks, 400 mg BID may be restarted and a repeat ECG must be performed 7 days following the dose adjustment. If upon re-exposure, QTcF exceeds 480 ms, discontinue nilotinib and a repeat ECG must be performed 7 days following discontinuation.
LVEF	
Grade 2	Monitor by ECHO First occurrence[a] at 400 mg BID: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level Recurrence[b] at 400 mg BID: Hold until event is ≤ grade 1, or has returned to baseline Resume at 400 mg QD Recurrence[b] at 400 mg QD: Discontinue nilotinib
Grade 3	Monitor by ECHO First occurrence[a] at 400 mg BID: Hold until event is ≤ grade 1, or has returned to baseline Resume at 400 mg QD Recurrence[b] at 400 mg QD: Discontinue nilotinib
Grade 4	Discontinue nilotinib
Hematologic Toxicity	
***Drug-Related* ANC/platelets**	
≥ Grade 3	First occurrence[a] at 400 mg BID: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level if recovery occurs within 14 days If recovery takes more than 14 days or recurs at 400 mg BID: Hold until event is ≤ grade 1, or has returned to baseline Resume at 400 mg QD Recurrence[b] at 400 mg QD: discontinue nilotinib

Toxicity	Modification

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BID = twice daily; CT = computed tomography; LVEF = left ventricular ejection fraction; QD = once daily; QTc = rate-corrected QT interval; ULN = upper limit of normal.

a "Occurrence" means the first time an AE is encountered by a patient at a given dose level.

b "Recurrence" means the second time an AE is encountered by a patient at a given dose level.

14.4.2.2 Dose Modifications for Arterial Occlusive Events and Venous Thrombotic/Embolic Events

If a serious arterial occlusive or venous thrombotic/embolic adverse reaction occurs, treatment should be interrupted. Neither ponatinib nor nilotinib should be readministered to patients with AOEs or VTEs unless the potential benefit outweighs the risk of recurrent AOEs or VTEs.

AOEs and VTEs include a broad range of nonspecific terms that could meet the criteria for diagnosis of this type of event. Investigators should use their clinical judgment and medical knowledge of the specific terms in describing these AOEs and VTEs.

Investigator discretion should be used to judge the event as a vascular pathology when applying these dose-modifying schemes.

14.4.2.2.1 Arterial Occlusive Events

In patients suspected of developing any arterial occlusive event, ponatinib or nilotinib should be immediately interrupted.

Patients should be discontinued from ponatinib or nilotinib in the event of MI, unstable angina, cerebrovascular accident, TIA, or revascularization procedures.

For all other arterial occlusive events, dose modification guidelines are outlined in Table 9 for ponatinib and Table 10 for nilotinib.

Table 9 Dose Modifications for Arterial Occlusive Events for Patients on Ponatinib

Arterial Occlusion: Cardiovascular and Cerebrovascular Events[a]	
Grade 1	Consider interruption or dose reduction of ponatinib until the event resolves, then resume at current dose.
Grade 2	First occurrence[b] at any dose level: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level. Recurrence[c] at 30 mg: Discontinue ponatinib Recurrence[c] at 15 mg: Discontinue ponatinib Recurrence[c] at 10 mg: Discontinue ponatinib
Grade 3 and 4	Discontinue ponatinib.
Other Arterial Occlusions including Peripheral Vascular Events	
Grade 1	Consider interruption or dose reduction of ponatinib until the event resolves, then resume at current dose.
Grade 2	First occurrence[b] at any dose level: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level Recurrence[c] at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Recurrence[c] at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Recurrence[c] at 10 mg: Discontinue ponatinib
Grade 3	Occurrence[b] at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Occurrence[b] at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Occurrence[b] at 10 mg: Discontinue ponatinib Any recurrence[c] at any dose level, discontinue ponatinib
Grade 4	Discontinue ponatinib

a Patients should be discontinued from ponatinib in the event of myocardial infarction (MI), unstable angina, cerebrovascular accident or transient ischemic attack (TIA), or revascularization procedures.
b "Occurrence" means the first time an AE is encountered by a patient at a given dose level.
c "Recurrence" means the second time any AOE, not necessarily recurrence of the same AOE, is encountered by a patient at any dose level.

Table 10 Dose Modifications for Arterial Thrombotic or Occlusive Events in Patients on Nilotinib

Arterial Occlusion: Cardiovascular and Cerebrovascular Events[a]	
Grade 1	Consider interruption or dose reduction of nilotinib until the event resolves.
Grade 2	First occurrence[b] at 400 mg BID: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level Recurrence[c] at 400 mg BID: Hold until event is ≤ grade 1, or has returned to baseline Resume at 400 mg QD Recurrence[c] at 400 mg QD: Discontinue nilotinib
Grade 3 and 4	Discontinue nilotinib
Other Arterial Occlusions including Peripheral Vascular Events	
Grade 1	Consider interruption or dose reduction of nilotinib until the event resolves.
Grade 2	First occurrence[b] at 400 mg BID: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level Recurrence[c] at 400 mg BID: Hold until event is ≤ grade 1, or has returned to baseline Resume at 400 mg QD Recurrence[c] at 400 mg QD: Discontinue nilotinib
Grade 3	First occurrence[b] at 400 mg BID: Hold until event is ≤ grade 1, or has returned to baseline Resume at 400 mg QD Recurrence[c] at 400 mg QD: Discontinue nilotinib
Grade 4	Discontinue nilotinib

a Patients should be discontinued from nilotinib in the event of myocardial infarction (MI), unstable angina, cerebrovascular accident or transient ischemic attack (TIA), or revascularization procedures.
b "Occurrence" means the first time an AE is encountered by a patient at a given dose level.
c "Recurrence" means the second time any AOE, not necessarily recurrence of the same AOE, is encountered by a patient at any dose level.

14.4.2.2.2 Venous Thromboembolic Events

Venous thromboembolic events are associated with ponatinib therapy. Patients should be discontinued from study drug in the event of life-threatening pulmonary embolism or retinal vein thrombosis.

For all other venous thromboembolic events in patients taking ponatinib, dose modification guidelines are outlined in Table 11.

Table 11 Dose Modifications for Venous Thromboembolic Events for Patients on Ponatinib

Venous Thromboembolic Events	
Grade 1	Consider interruption or dose reduction of ponatinib until the event resolves.
Grade 2	First occurrence[a] at any dose level: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level Recurrence[b] at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Recurrence[b] at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Recurrence[b] at 10 mg: Discontinue ponatinib
Grade 3	Occurrence[a] at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Occurrence[a] at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Occurrence[a] at 10 mg: Discontinue ponatinib
Grade 4	Discontinue ponatinib

a "Occurrence" means the first time an AE is encountered by a patient at a given dose level.
b "Recurrence" means the second time any VTE, not necessarily recurrence of the same VTE, is encountered by a patient at any dose level.

14.4.2.3 Dose Re-Escalation after Resolution of Adverse Drug Reactions

The dose of ponatinib or nilotinib can be re-escalated from the reduced dose level to the previously administered dose level if either of the following criteria are met:

- All ≥ grade 2 nonhematologic toxicities have recovered to ≤ grade 1 for at least 1 month
- All ≥ grade 3 hematologic and nonhematologic toxicities have recovered to ≤ grade 2 and are manageable with supportive therapy

Patients may receive step-wise ponatinib dose escalations (eg, 10 mg QD to 15 mg QD to 30 mg QD) or nilotinib dose escalation up to the starting dose if the above criteria continue to be met. In no circumstances should a patient receive a dose higher than that patient's starting dose.

Note: Patients with grade ≥3 LV dysfunction, CHF, or AOE or VTE are not eligible for dose re-escalation after resolution of their symptoms.

14.5 Prior and Concomitant Treatment(s)/Therapy

All concomitant medications administered from the time of informed consent signature through 30 days after End-of-Treatment (either last dose of study drug or an investigator/patient decision to discontinue, whichever occurs later) are to be reported on the appropriate eCRF for each patient.

14.6 Permitted Treatment

All routine and appropriate supportive care (including receipt of blood products and hematopoietic growth factors) will be allowed during this study, as clinically indicated, and in accordance with standard-of-care practices. Clinical judgment should be utilized in the treatment of any AE experienced by an individual patient.

Information on all concomitant medications, administered blood products, and interventions occurring during the study must be recorded on each patient's eCRF. Among other treatments for concurrent illnesses, the following therapies are allowed:

- Medical or surgical treatment necessary for the patient's well-being
- Where appropriate, treatment with hematopoietic growth factors
- Where appropriate, hydroxyurea or anagrelide during the first cycle of study drug administration (concomitant use must be discontinued by the end of the first cycle in all patients, and is thereafter prohibited)

14.7 Prohibited Treatment(s)/Therapy

The following concurrent medications and treatments are prohibited:

- Other anticancer therapies, including other TKIs
- Other investigational drugs or devices
- Medications with a known risk of Torsades de Pointes or that prolong the QTcF interval (Appendix A)
- Strong CYP3A4 inhibitors (see Appendix B)
- Strong CYP3A4 inducers (see Appendix B)
- Herbal preparations or related over-the-counter preparations containing herbal ingredients
- Stem cell transplantation

Elective surgery requiring inpatient care should be postponed until study completion if possible.

14.8 Potential Drug Interactions

14.8.1 Potential Interactions with Ponatinib

In vitro studies demonstrate that human CYP3A4 is involved in the metabolism of ponatinib. Based on in vitro studies, drug-drug interactions due to either CYP inhibition or induction by ponatinib are highly unlikely in clinical studies using the recommended daily doses of 15 and 30 mg. A drug interaction study in healthy subjects was performed with a strong CYP3A4

inhibitor (ketoconazole). Co-administration of ponatinib and ketoconazole was found to increase ponatinib C_{max} and AUC by 47% and 78%, respectively.

Some medications associated with QT prolongation also interact with CYP3A4; medications that are associated with the prolongation of the QT interval may interact with ponatinib either directly or through a common interaction with CYP3A4. As discussed in Section 11.2 Exclusion Criteria, and Section 14.7 Prohibited Treatment(s)/Therapy, the use of medications that prolong the QTcF interval or strong inhibitors or inducers of CYP3A4 is prohibited.

14.8.2 Potential Interactions with Nilotinib

Nilotinib is metabolized by CYP3A4 and is a substrate for P-gp. Therefore, absorption and subsequent elimination of systemically absorbed nilotinib may be influenced by substances that affect CYP3A4 and/or P-gp. When administered with ketoconazole, a strong CYP3A4 inhibitor, nilotinib exposure increased 3-fold. When co-administered with rifampicin, a strong CYP3A4 inducer, the C_{max} and AUC of nilotinib decreased by 64% and 80%, respectively. Additional studies have shown insignificant changes in nilotinib concentrations when administered with esomeprazole, an antacid, and a H2 blocker (famotidine given 10 hours before and 2 hours after dose of nilotinib).

14.9 Treatment Supply

14.9.1 Formulation, Packaging, and Labeling

14.9.1.1 Ponatinib

Ponatinib investigational drug product is supplied as tablets. Each tablet contains nominally 10 mg, 15 mg or 30 mg of ponatinib active ingredient. Other ingredients are typical pharmaceutical excipients which consist of: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, and film-coating. Film coating is comprised of: polyethylene glycol, talc, polyvinyl alcohol, and titanium dioxide. Tablets will be supplied as follows:

10 mg tablets: 30 count in white high-density polyethylene (HDPE) bottles with foil induction seal and cap

15 mg tablets: 30 count or 60 count in white HDPE bottles with foil induction seal and cap

30 mg tablets: 30 count in white HDPE bottles with foil induction seal and cap

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 tablets, and lot number.

14.9.1.2 Nilotinib

Commercially available nilotinib, which will be used in this study and will be supplied by the sponsor, is in capsule form. Each capsule contains 200 mg of nilotinib as hydrochloride monohydrate. Other ingredients are lactose monohydrate, crospovidone, poloxamer 188, colloidal anhydrous silica, magnesium stearate, gelatin, titanium dioxide, yellow iron oxide, shellac, and red iron oxide. Capsules are packaged as follows:

200 mg capsules: 28-count blister packs or bottles, depending on local supply form

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, and lot number.

14.9.2 Treatment Storage, Dispensing, and Accountability

The recommended storage condition for ponatinib and nilotinib is ≤30°C.

The study pharmacist or designee at the investigative 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. Supply shipping will be managed by an interactive voice response system (IVRS). The site must use either an appropriate dispensing log/accountability form provided by the sponsor, or an acceptable substitute. Each time study medication is dispensed for a patient, the following information is recommended to be recorded: the patient's initials, the patient's study number, dosage strength, the number of tablets or capsules 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. The investigator is responsible for ensuring that the patient diary card(s) and study drug provided to the patient and returned from the patient are accounted for and noted in source documentation.

14.9.2.1 Disposition of Used Supplies

All used bottles or packs 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 study and at termination, patients must return all unused study drug supplies and the return of these unused study drug supplies must be recorded. Returned supplies must not be re-dispensed.

No other utilization of ponatinib or nilotinib 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.

14.9.2.2 Inventory of Unused Supplies

Periodically, throughout and at the conclusion of the study, a representative of the sponsor will conduct an inventory of unused study drug. At the completion of the study, a final study drug accountability review will be conducted. Any discrepancies must be investigated and all unused

study drug must be destroyed on site per the standard operating procedures of the investigative site.

15 ADVERSE EVENT REPORTING

15.1 Adverse Events

15.1.1 Adverse Event Definition

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have 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 that sign, symptom, or disease is considered related to the medicinal product. Any worsening of a preexisting condition that is temporally associated with the use of the study drug (eg, occurs after the first dose of study drug), is also defined as an AE.

Adverse events include:

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

Additionally, AEs may include signs or symptoms resulting from:

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

15.1.2 Abnormal Test Findings

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

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

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

15.1.3 Performing Adverse Events Assessments

All observed or volunteered AEs, regardless of dose cohort or suspected causal relationship to the investigational product, will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE (see Section 15.2.1) requiring immediate notification to ARIAD Pharmaceuticals, Inc (ARIAD) or its designated representative.

15.1.4 Reporting Period

All AEs (serious, non-serious, and AESIs) should be recorded on the AE eCRF for all patients beginning at the time of signing the informed consent form and concluding 30 days following the last dose of the assigned study 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 12.2.1 Screen Failures).

Any AEs (serious, non-serious and AESIs) 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.

15.1.5 Adverse Event Severity

The severity of AEs will be assessed according to the NCI CTCAE, v.4.0 (see Appendix C and the Study Reference Manual). If the AE is not defined in the CTCAE, the investigator will determine the severity of the event based on the following definitions:

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

15.1.6 Causality

The investigator's assessment of causality must be provided for all AEs (serious and nonserious). An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to the AE.

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

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

Definitely Not Related (not drug related)

- The patient did not receive study drug

OR

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

OR

- There is another obvious cause of the AE

Probably Not Related (not drug related)

- There is evidence of exposure to study drug

AND one of the following:

- There is another, more likely cause of the AE
- Dechallenge (if performed) is negative or ambiguous
- Rechallenge (if performed) is negative or ambiguous

Possibly Related (drug related)

- There is evidence of exposure to study drug

AND one of the following:

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

Probably Related (drug related)

- There is evidence of exposure to study drug

AND one of the following:

- The temporal sequence of the AE onset, relative to administration of study drug, is reasonable

- The AE is more likely explained by study drug than by another cause

Definitely Related (drug related)

- There is evidence of exposure to study drug

AND one of the following:

- The temporal sequence of the AE onset, relative to administration of 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

15.1.7 Study Drug Action Taken

The investigator will classify the study drug action taken with regard to the AE. The action taken should be classified according to the following categories:

- **Dose Not Changed:** Study drug dose not changed in response to an AE.
- **Dose Reduced:** Study drug dose reduced in response to an AE.
- **Drug Interrupted:** Study drug administration interrupted in response to an AE.
- **Drug Withdrawn:** Study drug administration permanently discontinued in response to an AE.
- **Not Applicable:** Action taken regarding study drug administration does not apply.

  "Not applicable" should be used in circumstances such as when the investigational treatment had been completed before the AE began, and there was therefore no opportunity to decide whether to continue, interrupt, or withdraw treatment.

15.1.8 Adverse Event Outcome

An AE should be followed until the investigator has determined and provided the final outcome. The outcome should be classified according to the following categories:

- **Recovered/Resolved:** Resolution of an AE with no residual signs or symptoms.
- **Recovered/Resolved With Sequelae:** Resolution of an AE with residual signs or symptoms.
- **Not Recovered/Not Resolved (Continuing):** Either incomplete improvement or no improvement of an AE, such that it remains ongoing.
- **Fatal:** Outcome of an AE is death. "Fatal" should be used when death is at least possibly related to the AE.
- **Unknown:** Outcome of an AE is not known (eg, a subject was lost to follow-up).

15.1.9 Expectedness

The expectedness of an SAE is assessed by the sponsor in the overall classification of SAEs for regulatory reportability. The current Investigator's Brochure will be used as the reference for determination of expectedness and risk assessment for ponatinib. The current SmPC for Tasigna (nilotinib) (Nilotinib SmPC, 2016) will be used as the reference for determination of expectedness for nilotinib.

15.2 Serious Adverse Events and Adverse Events of Special Interest

The definitions and reporting requirements of ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A, will be adhered to in this study.

15.2.1 Serious Adverse Event Definition

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

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

- *Death:* An AE that results in death is any patient death within 30 days of the last dose of study drug administration. The cause of death or AE that resulted in a fatal outcome is the SAE.
- *Life-threatening:* An AE that places the patient, in the view of the investigator or the sponsor, at immediate risk of death from the event as it occurred (ie, this does not include an event that, had it occurred in a more severe form, might have caused death).
- *Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions*: Any substantial disruption of a patient'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 this study is considered an SAE. A new cancer is a cancer that is histopathologically different than the cancer under study (ie, does not include metastatic or progressive disease).
- *Important medical event:* Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not result in death, be life-threatening, or require hospitalization. However, if it is determined that the event may jeopardize the patient and/or may require intervention to prevent one of the other outcomes listed in the definition above, that important medical event 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.

15.2.1.2 Progression of the malignancy under study

Worsening of signs and symptoms of the malignancy under study (including signs and symptoms of progression) 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.

15.2.1.3 Hospitalizations

AEs (reported from clinical studies) that require hospitalization or prolongation of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a health care facility meets these criteria. AEs that require emergency room care but 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:

- Care is hospice facilities
- Respite care
- Care in skilled nursing facilities
- Care in nursing homes
- Routine emergency room admissions
- Same-day surgeries (as outpatient/same-day/ambulatory procedures)

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

- Social admission (eg, patient has no place to sleep)
- Protocol-specified admission during a clinical study (eg, for a procedure required by the study protocol)
- Optional admission not associated with a precipitating AE (eg, for elective surgery that was planned prior to study enrollment [appropriate documentation is required for these cases])

15.2.2 Adverse Events of Special Interest

Arterial occlusive and venous thrombotic/embolic events have been identified as AESIs for ponatinib and will be evaluated for nilotinib as well in this study. These include arterial and venous thrombotic and occlusive adverse events that meet the criteria for SAEs, defined above in Section 15.2.1, as well as those AEs that do not meet the SAE criteria. These events have also been observed for nilotinib.

AESIs require ongoing monitoring by investigators and rapid identification and communication by the investigator to the sponsor. All AESIs, regardless of seriousness, must be reported to the sponsor within 24 hours by completion of the AE eCRF. The sponsor has determined that the events listed below are AESIs (see Section 15.2.3 for reporting responsibilities).

- Myocardial infarction (MI): The Third Universal Definition of Myocardial Infarction (Thygesen et al, 2012) is used to define MI (see below)
- Angina (newly diagnosed or worsening of existing or unstable angina)

- Coronary artery disease (CAD) (newly diagnosed or worsening of existing CAD) or symptoms that may reflect cardiovascular disease (Thygesen et al, 2012)
- Cerebrovascular ischemic disease including ischemic or hemorrhagic stroke, vascular stenosis, TIA, cerebrovascular occlusive disease documented on diagnostic neuroimaging, or symptoms that may reflect cerebrovascular disease (Easton et al, 2009)
- New onset or worsening of peripheral artery occlusive disease (eg, of the renal artery, mesenteric artery, or femoral artery) or symptoms that may reflect peripheral vascular disease
- Retinal vascular thrombosis, both venous and arterial
- Venous thromboembolism that could result in significant compromise of organ function or other significant consequences (eg, pulmonary embolism, portal vein thrombosis, or renal vein thrombosis), or symptoms that may reflect venous thrombosis

15.2.3 Reporting SAEs and AESI

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 or AESI (either serious or nonserious). This timeframe also applies to additional new information (follow-up) on previously reported SAEs or AESIs.

15.2.4 Information to be Provided by the Investigator for an SAE or AESI

The sponsor requires all of the following information about the patient and the event:

- Investigator identification
- Patient identification code (eg, sex, age, date of birth)
- Information on study drug (eg, study drug name, assigned cohort, start/stop date, dose and frequency of study drug administered, most recent administered dose)
- Description of event

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

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

15.2.5 Follow-up Information on an SAE or AESI

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 or AESIs, the investigator is obligated to pursue and provide information to the sponsor. In addition, an investigator may be requested by the sponsor to obtain specific information in an

expedited manner. This information may be more detailed than that captured on the AE form. In general, this information 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 also be provided.

Required Follow-up for SAEs or AESIs

Routine follow-up should be conducted through and including 30 days after the last administration of assigned study treatment in the study or the investigator/patient decision to discontinue treatment, whichever occurs later, in all patients in order to monitor for the occurrence of SAEs or AESIs. If an SAE or AESI continues after the 30-day evaluation period, the patient must be followed until the event resolves to baseline, stabilizes, or is considered to be chronic/irreversible. The medical monitor may specify a longer follow-up period if required to assure the safety of the patient.

15.3 Expedited Reporting of SUSARs

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.

15.4 Other Safety Issues

15.4.1 Pregnancy, Contraception and Breastfeeding

Females of childbearing potential and fertile males will be informed as to the potential risk of conception while participating in this study. Females of childbearing potential are required to use a highly effective form of contraception from randomization through at least 4 months after the end of treatment. Birth control methods considered highly effective are as follows:

- Systemic hormonal contraceptives used with an additional barrier method:
    - combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation:
        - oral
        - intravaginal

        - transdermal
    - progesterone-only hormonal contraception associated with inhibition of ovulation
        - oral
        - injectable
        - implantable
    - intrauterine hormone releasing system (IUS)
- Intrauterine device (IUD)
- Bilateral tubal occlusion
- Vasectomized sole sexual partner
- Sexual abstinence (when in agreement with preferred and usual lifestyle of participant)

A pregnancy test will be performed on each premenopausal female of childbearing potential within 7 days prior to first dose of ponatinib, and again at the End-of-Treatment visit. A negative pregnancy test must be documented prior to administration of study drug. Females of childbearing potential should be advised to take a pregnancy test if their period is late, and to inform their investigator of the result promptly.

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

The investigator must immediately report follow-up information to the sponsor regarding the course of the pregnancy, including perinatal and neonatal outcomes, 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, that event should be reported as an SAE.

Pregnancy outcomes must also 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.

It is not known whether ponatinib passes into the breast milk. Female patients should not breastfeed babies during ponatinib treatment.

15.4.2 Overdose

An overdose is defined as the accidental or intentional ingestion or infusion of any dose of study treatment that exceeds the dose described in the protocol. All overdoses should be recorded on the Overdose Form and forwarded to ARIAD Pharmacovigilance and Risk Management, or its designated representative, within 24 hours. An overdose should be reported even if it does not result in an AE. If an overdose results in an AE, the AE should be reported on the AE eCRF. The dose administered should be documented on the Study Drug Administration eCRF.

16 PLANNED STATISTICAL METHODS

16.1 General Considerations

For the purposes of this protocol and all analyses, unless otherwise specified, a month is defined as 28 days, the same length as a cycle of treatment for ponatinib or nilotinib.

In the phase 2 portion, eligible CP-CMP patients will receive ponatinib 15 mg QD. Upon achievement of MMR, patients will have their daily dose of ponatinib reduced to 10 mg. In the phase 3 portion, eligible CP-CML patients will be randomized to one of 3 cohorts (Cohort A: 30 mg ponatinib QD, Cohort B: 15 mg ponatinib QD, Cohort C: 400 mg nilotinib BID) in a 1:2:1 fashion. Upon achievement of MMR, patients assigned to ponatinib 30 mg will have their daily dose of ponatinib reduced to 15 mg, and patients assigned to ponatinib 15 mg will have their daily dose of ponatinib reduced to 10 mg. In the phase 3 portion, patients will be stratified by age at baseline (≥60 years versus <60 years) and best response to prior imatinib therapy (CCyR or ≤ 1% BCR-ABL1^{IS} or better yes/no).

16.2 Analysis Populations

Intention to Treat (ITT) Population: The ITT population includes all patients who are treated in (phase 2) or randomized to (phase 3) the study. Patients will be analyzed according to the treatment to which they were assigned. Patients who are subsequently determined to be assigned to an incorrect stratum will be analyzed according to the stratum to which they were assigned at randomization.

Full Analysis Set (FAS): The Full Analysis Set includes all patients in the ITT population as defined above who have b2a2/b3a2 BCR-ABL1 transcript types at study entry (patients for whom a BCR-ABL1^{IS} ratio can be determined).

Treated Population: The treated population for each cohort includes all patients who have received at least 1 dose of study drug. The primary analyses of safety will be based on the treated population.

Per-protocol Population: The per-protocol population includes all patients who are randomized, receive at least 1 dose of study drug, and have no major protocol violations that could be expected to impact response data, such as: failure to satisfy 1 or more eligibility criteria, administration of other anti-cancer therapy concurrent with study drug, and administration of incorrect dose (eg, dose that was not the one to which the patient was randomized). Major protocol violations will be finalized and documented prior to database lock.

16.3 Study Endpoints

Primary Endpoint in Phase 2 and Each Cohort in Phase 3

- Major molecular response by 12 months for each cohort

Key Secondary Endpoints to be Estimated (Phase 2) and Formally Tested Statistically (Phase 3)

Molecular Key Secondary Efficacy Endpoints

- MR3/MMR at 24 months
- MR4 at 24 months
- MR4.5 at 24 months
- MR1 (≤10% BCR-ABL1^{IS}) at 3 months

Cytogenetic Key Secondary Efficacy Endpoints

- MCyR by 12 months

- CCyR at 12 months

Other Secondary Endpoints in Phase 2 and Each Cohort in Phase 3

- CCyR by 12 months
- Molecular response rates: ≤ 1% BCR-ABL1^{IS}, MR3/MMR, at 3-month intervals, and MR4, MR4.5 at 3-month intervals other than 24 months
- Safety
  i. Arterial occlusive events and venous thrombotic/embolic events in each cohort
  ii. AEs in each cohort
  iii. SAEs in each cohort
- Time to response
- Duration of response:
  i. ≤ 1% BCR-ABL1^{IS} and MMR at 12, 18, and 24 months
  ii. MCyR at 12 and 24 months
  iii. Duration of response in responders
  iv. Duration of therapy
- Hematologic response rates: CHR
- Tolerability:
  i. Discontinuation due to AEs in each cohort
  ii. Dose reductions due to toxicity in each cohort
  iii. Dose interruptions in each cohort
- Progression to AP- or BP-CML
- Progression-free survival
- Overall survival

Exploratory Endpoints

CCI [redacted]

16.4 Determination of Sample Size

16.4.1 Phase 2

The primary endpoint will be MMR rate by 12 months. A sample size of 75 patients will distinguish a favorable MMR by 12 month rate of 40% from a null or an uninteresting MMR rate of 25%, with a nominal 80% power and a 2-sided type I error rate of 0.05 (equivalent to a 2-sided 0.025) using an exact binomial test.

16.4.2 Phase 3

Based on accumulating data from the 15 mg cohort in phase 2, the phase 3 design (including number of ponatinib cohorts) and/or sample size may be amended prior to enrollment of patients into the phase 3 portion of the study.

The primary endpoint for this study will be MMR rate by 12 months. The primary analysis of the primary endpoint of MMR will be performed using a 2-sided alpha = 0.024 for each comparison.

A sample size of 150 patients in each Cohort A and C (ponatinib 30 mg and nilotinib, respectively) will distinguish a favorable MMR rate of 45% for ponatinib from a null or an uninteresting MMR rate of 25% for nilotinib with a nominal 90% power to detect an improvement in MMR of 20%.

The sample size of 300 patients in Cohort B and 150 patients in Cohort C will distinguish a favorable MMR rate of 40% for ponatinib from a null or an uninteresting MMR rate of 25% for nilotinib with approximately 80% power to detect an improvement in MMR of 15%.

16.5 Efficacy Analysis

16.5.1 Definitions of Efficacy Endpoints

The primary and secondary efficacy endpoints are listed in Section 16.3. This section defines the endpoints themselves and the associated conditions defining loss of those endpoints. Additional details, including definitions of specific time points, will be provided in the SAP.

16.5.1.1 Molecular Response Definitions

Major molecular response (MMR) is defined as a ≤0.1% ratio of BCR-ABL1 to ABL1 transcripts on the international scale (BCR-ABL1^{IS}), measured by real-time quantitative PCR.

MR1 at 3 months is the proportion of patients achieving a ratio of ≤10% BCR-ABL1 to ABL1 transcripts on the international scale at 3 months.

Molecular response: ≤ 1% BCR-ABL1^{IS}**, MR4, and MR4.5** are defined as ≤1%, ≤0.01%, and ≤0.0032% BCR-ABL1^{IS}, respectively. In the case of undetectable BCR-ABL1 transcript levels, a minimum of 10,000 and 32,000 ABL1 copies must be present in order to be classified as MR4 and MR4.5, respectively.

Time to MMR is defined as the interval between the date of first dose (phase 2) or randomization date (phase 3) and the first date at which the criteria for MMR are met.

Duration of ≤ 1% BCR-ABL1^{IS}**/MMR/MR4/MR4.5** is defined as the interval between the first assessment at which the criteria for ≤ 1% BCR-ABL1^{IS}/MMR/MR4/MR4.5 are met until the earliest date at which loss of ≤ 1% BCR-ABL1^{IS}/MMR/MR4/MR4.5 occurs (see below), or the criteria for progression (see Section 16.5.1.4) are met. Patients remaining in/at ≤ 1% BCR-ABL1^{IS}/MMR/MR4/MR4.5 will be censored at the last date at which the criteria for ≤ 1% BCR-ABL1^{IS}/MMR/MR4/MR4.5 are met.

Loss of MMR is defined as an increase to >0.1% of BCR-ABL1^{IS}. This result must be confirmed at the subsequent visit, unless it is associated with confirmed loss of CHR, or loss of CCyR, or progression to AP- or BP-CML, or death due to CML.

Loss of ≤ 1% BCR-ABL1^{IS} is defined as an increase to >1% of BCR-ABL1^{IS}. This result must be confirmed at the subsequent visit unless it is associated with confirmed loss of CHR, or progression to AP- or BP-CML, or death due to CML.

Loss of MR4 is defined as an increase to >0.01% of BCR-ABL1^{IS}. This result must be confirmed at the subsequent visit, unless it is associated with confirmed loss of CHR, or loss of CCyR, or progression to AP- or BP-CML, or death due to CML.

Loss of MR4.5 is defined as an increase to >0.0032% of BCR-ABL1^{IS}. This result must be confirmed at the subsequent visit, unless it is associated with confirmed loss of CHR, or loss of CCyR, or progression to AP- or BP-CML, or death due to CML.

16.5.1.2 Cytogenetic Response Definitions

Rate of major cytogenetic response (MCyR) by 12 months is the proportion of patients achieving CCyR or PCyR at any time within 12 months after randomization.

Cytogenetic response is the percentage of Ph+ metaphases in bone marrow (peripheral blood may not be used), with a review of a minimum of 20 metaphases. Responses are defined as follows:

Major cytogenetic response (MCyR): CCyR or PCyR

- Complete cytogenetic response (CCyR): 0% Ph+ metaphases
- Partial cytogenetic response (PCyR): >0% to 35% Ph+ metaphases

Rate of complete cytogenetic response (CCyR) by 12 months is the proportion of patients achieving CCyR at any time within 12 months after first dose date (phase 2) or randomization (phase 3). Additionally, CCyR at 12 months will be calculated using only cytogenetic criteria. Additional analyses will be performed that will consider patients who achieve ≤ 1% BCR-ABL1^{IS} to have achieved CCyR.

Time to MCyR is defined as the interval from first dose date (phase 2) or randomization (phase 3) until the criteria for MCyR are first met.

Duration of MCyR is defined as the interval between the first assessment at which the criteria for MCyR are met until the earliest date at which loss of MCyR occurs, or the criteria for progression (Section 16.5.1.4) are met. Patients remaining in response will be censored at their latest assessment (either cytogenetic or molecular).

Loss of MCyR is defined as a single BM assessment with Ph+ metaphases >35% after achievement of MCyR (CCyR or PCyR or ≤ 1% BCR-ABL1^{IS})

Loss of CCyR is defined as either an increase in the Ph+ metaphases in BM to >0% in a single BM assessment, defined in Section 16.5.1.1.

Loss of PCyR is defined as an increase in the Ph+ metaphases in BM from >0% to 35% to >35% in a single BM assessment.

16.5.1.3 Hematologic Response Definitions

Complete hematologic response (CHR) rate is defined as the proportion of patients achieving CHR at any time after initiation of study treatment. CHR will be confirmed no earlier than 28 days later.

CHR is defined as achieving all of the following measurements:

- White blood cells (WBC) ≤ institutional ULN
- Platelets <450 x 10^9/L
- No blasts or promyelocytes in peripheral blood
- <5% myelocytes plus metamyelocytes in peripheral blood
- Basophils in peripheral blood <5%
- No extramedullary involvement (including no hepatomegaly or splenomegaly)

Loss of CHR is defined as the appearance of any of the following, confirmed by a second assessment at least 4 weeks later (unless associated with progression [Section 16.5.1.4] or CML-related death):

- WBC count that rises to >20 x 10^9/L
- Platelet count that rises to ≥600 x 10^9/L
- Progressing splenomegaly to a size ≥5 cm below the left costal margin
- Appearance of ≥5% myelocytes plus metamyelocytes in peripheral blood
- Appearance of blasts or promyelocytes in the peripheral blood

16.5.1.4 Event-Related Definitions

Progression-free survival (PFS) is defined as the interval between the first dose date of study treatment and the first date at which the criteria for progression are met (progression to AP- or BP-CML), or death due to any cause, censored at the last response assessment.

Progression to AP-CML is defined as:

- ≥15% and <30% blasts in peripheral blood or bone marrow

or

- ≥20% basophils in peripheral blood or bone marrow

or

- ≥30% blasts + promyelocytes in peripheral blood or bone marrow (but <30% blasts)

or

- <100 x 10^9 platelets/L in peripheral blood unrelated to therapy

or

- Cytogenetic, genetic evidence of clonal evolution

and

- No extramedullary disease

Progression to BP-CML is defined as:

- ≥30% blasts in peripheral blood or bone marrow

or

- Extramedullary disease other than hepatosplenomegaly

Overall survival (OS) is defined as the interval between the first dose date of study treatment and death due to any cause, censored at the last contact date to be alive.

16.5.2 Primary Endpoint Analysis

For the phase 2 portion, the primary analysis of the primary endpoint will be performed using an exact binomial confidence interval for the MMR rate by 12 months on the ITT population. A sample size of 75 patients will distinguish a favorable MMR by 12 month rate of 40% from a null or an uninteresting MMR rate of 25%, with a nominal 80% power and a 2-sided type I error rate of 0.05 (equivalent to a 2-sided 0.025). Using the 25% boundary for MMR, 27 or more MMR responders will be needed for a lower limit of the 2-sided exact 95% CI for the MMR rate to exceed 25%.

For the phase 3 portion, the primary analysis of the primary endpoint will be performed using a stratified Cochran Mantel-Haenszel (CMH) test. The phase 3 portion will be stratified by age at baseline (≥60 versus <60 years) and best response to prior imatinib therapy (CCyR or ≤ 1% BCR-ABL1^{IS} or better, yes/no) to compare the MMR rate by 12 months between patients receiving either dose level of ponatinib (initial dose: 30 mg once daily [QD] or 15 mg once daily [QD]) and patients receiving nilotinib (initial dose: 400 mg BID) and will follow a testing procedure to ensure an overall 2-sided Type I error rate of <0.05 (see Section 16.11).

The primary analysis for phase 3 will be based on the Full Analysis Set (all patients randomized to a treatment group for whom a BCR-ABL1^{IS} ratio can be determined at baseline). A sensitivity analysis of the primary endpoint will be performed on the ITT population, with patients not evaluable treated as nonresponders.

16.5.2.1 Data Handling Rules for the Primary Analyses of the Primary Endpoint

The following patients will be analyzed as responders in the primary analysis:

- Patients who meet the criteria for MMR by 12 months after randomization

All other patients will be analyzed as non-responders in the primary analysis, including treated (phase 2) or randomized (phase 3) patients without follow-up (and any patients who meet the criteria for MMR at study entry).

16.5.3 Secondary Efficacy Endpoint Analyses

16.5.3.1 Key Secondary Efficacy Endpoints

For the phase 2 portion, key secondary endpoints will be performed on the ITT population. Sensitivity analyses of molecular key secondary endpoints may be performed on the Full Analysis Set. Note that at some analysis time points not all key secondary endpoints will be mature (eg, molecular key secondary endpoints will not be mature at interim analysis or 12 month analysis – see Section 16.5.3.3 for the statistical handling of these key secondary endpoints). In addition to the final analyses of key secondary endpoints, an interim analysis will be performed after 50 patients reach 6 months of treatment (see Section 16.11.1).

For the phase 3 portion, formal statistical analyses will be performed on the following molecular key secondary endpoints (MR3/MMR at 24 months; MR4 at 24 months; MR4.5 at 24 months, MR1 at 3 months) and key secondary cytogenetic endpoints (CCyR at 12 months; MCyR by 12 months). Comparisons of molecular key secondary endpoints and cytogenetic key secondary endpoints will be performed separately. Analyses of molecular key secondary endpoints will be performed on the Full Analysis Set. Analyses of cytogenetic key secondary endpoints will be performed on the ITT population. For each dose comparison (within a given set of key secondary endpoints) that is significant in the primary analysis, formal statistical comparisons of key secondary endpoints will be performed using a closed testing procedure according to the ranking below and will take place only if comparisons of all other secondary efficacy endpoints with a smaller rank are significant at the 2-sided 0.025 level (molecular endpoints and cytogenetic endpoints will be tested separately, thus the significance level has been halved). Note that at some analysis time points not all key secondary endpoints will be mature (eg, molecular key secondary endpoints will not be mature at interim analysis or 12 month analysis – see Section 16.5.3.3 for the statistical handling of these key secondary endpoints). Each sequence of key efficacy endpoints will be tested separately for each treatment comparison (Cohort A versus Cohort C, Cohort B versus Cohort C), within the sets of molecular and cytogenetic endpoints, respectively.

Molecular Key Secondary Efficacy Endpoints to be Formally Tested Statistically in Phase 3

- MR3/MMR at 24 months
- MR4 at 24 months
- MR4.5 at 24 months
- MR1 (≤10% BCR-ABL1^{IS}) at 3 months

Cytogenetic Key Secondary Efficacy Endpoints to be Formally Tested Statistically in Phase 3

- CCyR at 12 months
- MCyR by 12 months

The additional key secondary efficacy endpoints to be tested are listed below. These will not be subject to formal statistical testing.

- Molecular response rates: ≤ 1% BCR-ABL1^{IS}, MR3/MMR, at 3-month intervals, and MR4, MR4.5 at 3-month intervals other than 24 months
- CCyR by 12 months
- Time to response
- Duration of response:
  i. ≤ 1% BCR-ABL1^{IS} and MMR at 12, 18, and 24 months
  ii. MCyR at 12 and 24 months
  iii. Duration of response in responders
  iv. Duration of therapy
- Progression-free survival

- Overall survival

16.5.3.2 Analysis Methods for Secondary Efficacy Endpoints

For the phase 2 portion, the analysis of the secondary efficacy endpoints of molecular response rates, cytogenetic response rates, CHR rate and rate of progression to AP or BP CML will be performed using an exact binomial confidence interval on the ITT population. For the phase 3 portion, the analysis of the secondary efficacy endpoints of molecular response rates, cytogenetic response rates, CHR rate and rate of progression to AP- or BP-CML will be performed using a stratified CMH test. For both phases, PFS and OS will be analyzed using the Kaplan-Meier method. Descriptive statistics will be provided for duration of response in responders and duration of therapy.

For the phase 3 portion, analyses of molecular response rates will be performed on the Full Analysis Set. All other analyses will be performed on the ITT population.

16.5.3.3 Data Handling Rules for Secondary Efficacy Endpoint Analyses

For the secondary endpoints of cytogenetic responses, at any given cytogenetic assessment after baseline, if fewer than 20 metaphases are examined, the rules in Table 12 will apply to the determination of MCyR:

Table 12 Determination of MCyR by Cytogenic Assessment

Number of metaphases examined	≤12	13	14	15	16	17	18	19
Number of Ph+ cells	Any number	0	≤1	≤2	≤3	≤4	≤5	≤6
% Ph+	--	0%	≤7%	≤13%	≤19%	≤24%	≤28%	≤32%
Response	Not Evaluable	PCyR	PCyR	PCyR	PCyR	PCyR	PCyR	PCyR

Ph+ = Philadelphia chromosome positive; PCyR = partial cytogenetic response

Determination of CCyR by cytogenetic assessment will require at least 20 metaphases examined.

For the analyses of secondary endpoints of MCyR, CCyR, ≤ 1% BCR-ABL1^{IS}, MR4.5, MR4, and CHR, if patients do not have a baseline assessment or post-baseline response assessment, the patients will be considered as non-responders. Patients who meet the criteria for response at baseline will also be analyzed as non-responders.

16.5.4 Subgroup Analyses of the Primary Endpoint and Secondary Efficacy Endpoints

For the primary endpoint and secondary efficacy endpoints, subgroup analyses will be performed by baseline potential prognostic factors when warranted based on numbers of patients in subgroups (details will be included in the Statistical Analysis Plan [SAP]). Subgroups may include:

- Age (<60, ≥60 years)
- Gender
- Race
- Geographic region

- T315I mutation history (Yes, No)
- Best response to prior imatinib therapy (CCyR, ≤ 1% BCR-ABL1^{IS} or better)
- Other disease-related prognostic factors

16.6 Safety Analysis (Phase 2 and Phase 3)

All patients receiving at least one dose of study drug will be considered evaluable for safety. Safety analyses will be performed based on the treated population. All AEs with an initial onset date on or after the first dose date and no later than 30 days after the last dose date of study treatment or events starting after initial consent that worsen in severity on or after the first dose date will be considered treatment-emergent. AEs and SAEs will be summarized for treatment-emergent adverse events (TEAEs) and all AEs will be listed.

16.6.1 Analysis of Arterial Occlusive and Venous Thrombotic/Embolic Events

Number and percentages of patients who develop arterial occlusive and venous thrombotic/embolic events will be summarized for the single arm in phase 2 and each cohort in phase 3. The arterial occlusive and venous thrombotic/embolic events will be categorized as follows:

- Arterial occlusive events
  i. Cardiovascular occlusive events
  ii. Cerebrovascular occlusive events
  iii. Peripheral vascular occlusive events
- Venous thromboembolic events

Details for classification of specific events as arterial occlusive and venous thrombotic/embolic events are given in Section 14.4.1.1.

The primary analysis of arterial occlusive events and venous thromboembolic events will be an exposure-adjusted incidence rate, as follow-up may differ among the cohorts. The exposure-adjusted incidence rate is calculated as number of patients with the AE divided by total treatment exposure time. Further description of methods of calculating exposure time will be documented in the statistical analysis plan.

The following additional descriptive analyses will be performed to characterize arterial occlusive and venous thrombotic/embolic events:

- Time to onset: calculated as date of first arterial occlusive or venous thrombotic/embolic adverse event – first dose date + 1
- Dose at onset: dose of ponatinib or nilotinib taken immediately prior to onset of first arterial occlusive or venous thrombotic/embolic event.

Detailed data handling rules will be specified in the SAP for incomplete or missing onset dates.

Baseline risk factors for the occurrence of arterial occlusive or venous thrombotic/embolic events will be evaluated for all patients, and will include:

- History of arterial occlusive disease

- History of other cardiovascular disease
- History of venous thromboembolism
- Hypertension
- History of diabetes/hyperglycemia
- History of smoking
- Obesity
- History of hyperlipidemia
- Age
- Gender
- Other risk factors

16.6.2 Analysis of Categories of Adverse Events

Categories of AEs will be prospectively defined using Standardized MedDRA Queries (SMQs) or Modified MedDRA Queries based on SMQs and MedDRA System Organ Classes (SOCs). The AE crude rates, as well as the frequency of occurrence by overall toxicity, categorized by toxicity grades (severity) will be described for the single arm in phase 2 and each cohort in phase 3. Events will also be characterized by time to onset, dose at onset, and duration as described above. Further details will be outlined in the SAP.

16.6.3 Other Safety Analyses

For all treatment-emergent AEs and SAEs, crude rates as well as the frequency of occurrence by overall toxicity, categorized by toxicity grades (severity) will be described for each cohort. Listings of laboratory test results will be generated, and shift in laboratory parameters from baseline to worst post-baseline value in terms of CTCAE grades will be summarized. Maximum shift from baseline in blood pressure and mean change from baseline over time will be summarized. Exposure to study drug over time will also be summarized.

16.6.4 Analysis of Treatment Discontinuation Rate due to AEs, Dose Reductions, and Dose Interruptions

For the single arm in phase 2 and each dose cohort in phase 3, numbers and percentages of patients who discontinue treatment due to AEs, who have any dose reduction from the starting dose due to AEs or who have dose interruption of at least 3 days will be provided. Number of days at each dose level and time to first dose reduction due to AE will be summarized to characterize length of dose interruptions and reductions.

16.7 Exposure-Response Analysis

Analyses of the relationship between ponatinib exposure and efficacy (MMR, MCyR, and $\leq 1\%$ BCR-ABL1^{IS}) and safety measures (including at a minimum AOEs and VTEs and events occurring in at least 30 patients), will be undertaken. Logistic regression models and Cox regression models will be used for the binary outcomes, with exposure as a time varying covariates. Further detail will be summarized in the SAP.

16.8 Quality of Life / Health Outcomes Analysis

CCI [redacted]

16.9 Exploratory Biomarker Analyses

CCI [redacted]

16.10 Protocol Deviations/Violations

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

16.11 Interim Analysis

16.11.1 Phase 2

An interim efficacy analysis will be performed after 50 patients reach 6 months of treatment. A sample size of 50 patients will distinguish a favorable $\leq 1\%$ BCR-ABL1^{IS} by 6 month rate of 50% from a null or an uninteresting $\leq 1\%$ BCR-ABL1^{IS} rate of 25%, with a nominal 96% power and a 2-sided type I error rate of 0.05 (equivalent to a 2-sided 0.025) using an exact binomial test. At the interim analysis, the CI for the $\leq 1\%$ BCR-ABL1^{IS} rate will be calculated. In the PACE (AP24534-10-201) trial, molecular responses at early time points were shown to be predictive of deeper molecular responses at later time points. Therefore, it is expected that $\leq 1\%$ BCR-ABL1^{IS} by 6 months is expected to be a good surrogate for the primary endpoint of this study - MMR by 12 months. If there are fewer than 20 $\leq 1\%$ BCR-ABL1^{IS} responders at the interim analysis, consideration may be given to terminating the study. Favorable results from this interim analysis may allow the Sponsor to accelerate the implementation of the Phase 3 portion of this study.

16.11.2 Phase 3

An efficacy interim analysis is planned after the first 300 randomized patients have at least 12 months of follow-up. To maintain an overall Type I error rate of 0.05 (2-sided), an O'Brien-Fleming approach will be used which requires a two-sided p-value <0.0052 at the interim (at 50% of information time). Thus, with 2 treatment comparisons significance will be declared for any arm where the 2-sided p-value is <0.0026. For each dose comparison, if this boundary is not crossed at the time of the interim analysis, then the primary analysis will be conducted 12 months following the last patient randomized. A Bonferroni procedure will be used to adjust

for comparisons of Cohorts A and B to Cohort C, with a dose considered significant if the 2-sided p-value is <0.024.

Impact on Study Conduct and Secondary Endpoints (Phase 3)

The phase 3 design may be modified based on accumulating data from the 15 mg cohort in phase 2 before enrolling new patients.

It is expected that the study will be fully enrolled prior to the conduct of the interim analysis and the interim analysis will not affect enrollment or continuity of therapy. In the event that the study crosses the efficacy boundary at the interim analysis, we would expect to continue patients on their randomized treatment arm to allow for continued assessment of other time points and the secondary efficacy endpoints. The key secondary efficacy endpoints will not be mature at the time of the interim analysis (see Section 16.5.3.1). For each dose comparison that is significant in the primary analysis, these endpoints will be considered significant if they reach a nominal significance level of 0.001 two-sided, otherwise they will be tested at 0.025 two-sided when mature for the molecular and cytogenetic sets of key secondary endpoints, respectively, in the order defined in the closed testing procedure described in Section 16.5.3.3. Additionally, at the time the primary analysis becomes significant, conditional power will be calculated for the secondary endpoints that have not yet matured. The main conditional power calculations will assume the observed effect continues, and sensitivity analyses will also be conducted using the boundaries of 80% and 95% confidence intervals on the observed effect. Because these confidence intervals will likely be wide, it would be expected that the conditional power might vary widely.

17 QUALITY CONTROL AND QUALITY ASSURANCE

The sponsor performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any patients into this study, the sponsor personnel or its designee and the investigator will review the protocol, the Investigator's Brochure, the electronic Case Report Forms (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.

17.1 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 accepts the responsibility. The sponsor must be notified in writing and must agree to the change in advance. An updated FDA Form 1572 will be filed with the sponsor for any changes in the study personnel reported in the current FDA Form 1572.

17.2 Study Monitoring

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

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

18 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 GCP guidelines and the applicable regulatory requirements.

18.1 Institutional Review Board or Ethics Committee 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 should also be reviewed by the IRB/EC. The sponsor will not ship clinical supplies until a signed approval letter from the IRB/EC has been received and a Clinical Trial Agreement has been signed by the sponsor and the clinical site.

18.2 Patient Information and Consent

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

A copy of the study site's proposed informed consent document should be submitted to the sponsor for review and comment before submission to the IRB/EC. The study should not begin until the document has been reviewed by the sponsor and must not begin until the document has been approved by the IRB/EC. In some instances, the study must not begin until the document has been approved by a regulatory agency.

The informed consent document shall contain all of the elements of the informed consent specified in the regulations. Some regulations may require the disclosure of additional information to the patient and/or inclusion of additional information in an informed consent document.

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.

18.3 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.

18.4 Study Committees

18.4.1 Data Monitoring Committee

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

The DMC will be responsible for evaluating the results of safety analyses and will make recommendations to the sponsor. Efficacy data can also be requested, if needed, to evaluate risk/benefit before making a recommendation. The DMC will operate under the DMC charter, which specifies the data to be included in each review, rules related to study modification, and protection of the integrity of the data. At each meeting, the DMC will make recommendations to either continue the study unchanged, to modify the study, or to discontinue the study. The DMC will communicate the recommendations to the sponsor. The final decision to act on the DMC recommendations will be made by the sponsor in consultation with the Study Steering Committee. An independent committee may be installed to assess cardiovascular events and other related safety concerns as appropriate.

18.4.2 Study Steering Committee

A study steering committee will be constituted with initiation of the study. Its purpose is to function in an advisory capacity to: 1) provide input on study conduct and progress; 2) ensure scientific and ethical integrity of the study; and 3) provide ongoing oversight of safety and efficacy in this open-label study. The study steering committee will include clinicians expert in

the clinical care and investigation of the targeted patient population, and will also include sponsor representatives. In addition to general study oversight, it will be responsible for periodic review of study data to evaluate the safety profile of ponatinib, assess accumulating signals of efficacy, evaluate data quality, and provide input on operational aspects of the study. The study steering committee may make recommendations for the sponsor's consideration based on periodic review.

19 DATA HANDLING AND RECORD KEEPING

19.1 Case Report Forms and Study Records

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

19.2 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.*

19.3 Retention of Data

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

19.4 Termination of Study

The sponsor may terminate the study or a study site 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

20 FINANCING AND INSURANCE

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

21 PUBLICATION AND DISCLOSURE POLICY

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

Section 801 of the FDA Amendments Act mandates the registration with ClinicalTrials.gov of certain clinical studies of drugs (including biological products) and medical devices subject to FDA regulations for any disease or condition. The International Committee of Medical Journal Editors requires study registration as a condition for publication of research results generated by a clinical study (http://www.icmje.org [Accessed: 21 March 2015]).

The institution and principal investigator acknowledge that the study is a multi-center study, and, as such, agree that they will not publish a manuscript, 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 submitted 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 institution's right to publish with ARIAD's proprietary interests, the institution will submit to ARIAD material intended for publication, manuscripts, 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 an institution and/or principal investigator publishes the results of the study, the institution and/or principal investigator hereby grant ARIAD an irrevocable, royalty-free license to make and distribute copies of such publication under any copyright privileges that the institution and/or principal investigator may have.

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23 APPENDICES

APPENDIX A Drugs with a Risk of Torsade de Pointes

Four categories of QT-prolonging drugs that may be used as a guide for this protocol can be accessed at http://www.crediblemeds.org/everyone/composite-list-all-qtdrugs/ [Accessed: 21March 2014]. 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 Torsade de Pointes are the only category of QT-prolonging drugs that are prohibited in this study.

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

APPENDIX B Drugs that Interact with CYP3A4, 5, and 7

The list of drugs that interact with CYP3A4, 5, and 7 can be found online at http://medicine.iupui.edu/clinpharm/ddis/table.aspx [Accessed 21 March 2015]. Drugs listed as strong inhibitors and inducers of CYP3A should be avoided, if possible.

Note: The website should be used as a guideline and is not necessarily comprehensive. It is the investigator's responsibility to ensure that any drugs under consideration have not been newly identified as strong CYP3A4/5 inhibitors or inducers.

APPENDIX C National Cancer Institute Common Terminology Criteria for Adverse Events

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 21 Mar 2014].

This version of CTCAE is compatible at the AE term level where each CTCAE term is a Medical Dictionary for Regulatory Activities Terminology Lowest Level Term (MedDRA LLT). CTCAE version 4.0 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).

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Clinical VP Approval	14-Mar-2017 17:03 GMT-04