Title: A Randomized, Open-label, Phase 2 Trial of Ponatinib in Patients with Resistant Chronic Phase Chronic Myeloid Leukemia to Characterize the Efficacy and Safety of a Range of Doses

NCT Number: NCT02467270

Protocol Approve Date: 05 October 2020

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

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

CLINICAL STUDY PROTOCOL

Study Title:	A Randomized, Open-label, Phase 2 Trial of Ponatinib in Patients with Resistant Chronic Phase Chronic Myeloid Leukemia to Characterize the Efficacy and Safety of a Range of Doses
Protocol Number:	AP24534-14-203
Study Phase:	2
Product Name:	Ponatinib
IND Reference Number:	78,375
EudraCT Number:	2014-001617-12
Sponsor:	ARIAD Pharmaceuticals, Inc. (a wholly-owned subsidiary of Takeda Pharmaceutical Ltd. Co.) 40 Landsdowne Street, Cambridge, MA 02139 USA Telephone: +1 (617) 679-7000
Protocol Issue Date:	05 October 2020
Version Number:	Version 7.0

PROTOCOL REVISION HISTORY:

Amendment Number	Protocol Version Number	Date
Original Protocol	Version 1.0	02 February 2015
Amendment 1	Version 2.0	17 December 2015
Amendment 1.1	Version 2.1 (Norway)	18 December 2015
Amendment 1.2	Version 2.2 (Germany)	16 February 2016
Amendment 2	Version 3.0	30 March 2016
Amendment 2.1	Version 3.1 (Norway)	06 June 2016
Amendment 3	Version 4.0	30 May 2017
Amendment 4	Version 5.0	01 March 2018
Amendment 5	Version 6.0	18 April 2019

Amendment Number	Protocol Version Number	Date
Amendment 6	Version 7.0	05 October 2020

2 SIGNATURE PAGES

2.1 Signatory*

PPD

*The protocol will be approved electronically in Takeda Pharmaceutical Ltd. Co.'s Electronic Document Management System (Mosaic). 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. (a wholly-owned subsidiary of Takeda Pharmaceutical Ltd. Co.)

3 CONTACT INFORMATION

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Sponsor Medical Monitor:	PPD

4 PROTOCOL SYNOPSIS

Sponsor	ARIAD Pharmaceuticals, Inc. (a wholly-owned subsidiary of Takeda Pharmaceutical Ltd. Co.) 40 Landsdowne Street Cambridge, MA 02139 USA
Study Treatment	Ponatinib
Study Title	A Randomized, Open-label, Phase 2 Trial of Ponatinib in Patients with Resistant Chronic Phase Chronic Myeloid Leukemia to Characterize the Efficacy and Safety of a Range of Doses
Phase	Phase 2
Eligible Population	Patients with chronic phase chronic myeloid leukemia (CP-CML) who have received at least two prior tyrosine kinase inhibitor (TKI) therapies and have demonstrated resistance to treatment or have the T315I mutation
Summary and Study Rationale	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. The latter confers uniform resistance to all other available BCR-ABL inhibitors (e.g., imatinib, nilotinib, dasatinib, and bosutinib). Ponatinib (Iclusig®, ARIAD Pharmaceuticals, Inc.) is approved in the United States (US) for the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom no other TKI therapy is indicated and for treatment of adult patients with T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Ph+ ALL. In the European Union (EU), ponatinib is approved for the treatment of adult patients with CML (chronic phase, accelerated phase, or blast phase) and Ph+ ALL who are resistant to dasatinib (or nilotinib for CML), who are intolerant to dasatinib (or nilotinib for CML), and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation. The phase 2 clinical trial of ponatinib in patients with CML or Ph+ ALL who have had prior TKI therapy (AP24534-10-201, PACE), which supported the drug's approvals, tested a starting dose of 45 mg daily. The 5-year data from this study confirmed that treatment with ponatinib continued to provide clinically meaningful responses. In patients with CP-CML, the primary endpoint was met in more than double that of the most recent dasatinib or nilotinib therapy (55.4% vs. 25.8%) and 85.7% remained in the primary endpoint for ≥550 days at 30 mg. The median duration of follow-up was 37.3 months. 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. Current data suggest that a dose-effect relationship exists with efficacy and with the

	occurrence of AOEs, and that a lower daily dose may reduce the incidence of AOEs. This clinical study will assess the relationships of exposure with efficacy and safety: patients will receive a range of initial doses, and at defined time points, patients in response will undergo a dose reduction. The goal of the study will thus be to understand induction of responses, maintenance of responses, safety, and exposure-response as consequences of these dosing strategies. The primary endpoint of this study will be the achievement of ≤ 1% BCR-ABL1^{IS} at 12 months. This incorporates standard CML approaches to patient care and uses patient monitoring. Increasingly, patient monitoring is being performed by quantitation of BCR-ABL1 transcripts from a standard established by the international scale (IS) (Marin, 2014; NCCN, 2014; Baccarani et al, 2013; Marin et al, 2012; Lauseker et al, 2012; Saglio et al, 2012). This trial is being conducted in fulfillment of a Food and Drug Administration (FDA) post-marketing requirement (PMR2113-6).
Study Design	This is a multi-center, randomized phase 2 trial to characterize the safety and efficacy of ponatinib over a range of 3 starting doses. Eligible patients must have CP-CML; have received at least 2 prior TKI therapies and have demonstrated resistance to treatment or have the T315I mutation. Patients will be randomized to receive once-daily oral administration of 1 of 3 starting doses of ponatinib: 45 mg (Cohort A), 30 mg (Cohort B), or 15 mg (Cohort C). Patients starting at 45 mg or 30 mg will have their daily dose reduced to 15 mg upon achievement of ≤ 1% BCR-ABL1^{IS}, as defined in Section 14.1.3. The study will consist of an initial 24-cycle Main Treatment Period; additionally, the study includes an optional Treatment Continuation Period. All randomized patients will enter the Main Treatment Period and will remain on treatment in the Main Treatment Period until the occurrence of at least one of the following: absence of complete hematologic response (CHR) by 3 months, absence of major cytogenetic response (MCyR) at 12 months, absence of ≤ 1% BCR-ABL1^{IS} at 12 months, loss of ≤ 1% BCR-ABL1^{IS} as defined in Section 16.5.1.1, development of intolerance, or completion of all 24 cycles of treatment (whichever occurs first). Patients who achieve ≤ 1% BCR-ABL1^{IS} at any time point undergo dose reduction, and then lose ≤ 1% BCR-ABL1^{IS} are candidates for dose re-escalation to their starting dose, as described in Section 14.1.4. Following completion of the 24-month Main Treatment Period or following early withdrawal from the Main Treatment Period before completing all 24 cycles of the Main Treatment Period, patients who are both tolerating ponatinib treatment and receiving clinical benefit from treatment may enter into an optional Treatment Continuation Period upon discussion and agreement between the investigator and medical monitor. Examples of clinical benefit that could allow a patient to enter the Treatment Continuation Period include (but are not limited to) a reduction from baseline in BCR-ABL^{IS} levels (but without meeting the protocol-defined response criterion of ≤1% BCR-ABL1^{IS} at 12 months), an improvement in hematologic parameters (but without meeting the protocol-defined response criterion of CHR by 3 months), or a BCR-ABL^{IS} level indicative of clinical benefit (but that is > 1%, after loss of ≤ 1% BCR-ABL1^{IS} at an earlier time point). Each patient may remain on study treatment during the Treatment Continuation Period until the patient stops receiving clinical benefit or experiences unacceptable toxicity, or until the study is terminated by the sponsor (whichever occurs first). Section 12 describes follow-up and data collection for such continuation patients. Section 10.4 provides more detail about the study design including descriptions of the Main Treatment and Treatment

	Continuation Periods. The trial will assess hematologic response, cytogenetic response, and molecular response—as well as characteristics of efficacy, including time to and duration of responses—both by starting dose and after dose reduction. AE rates and the rates of AOEs and venous thrombotic/embolic events (VTEs), in particular, will be measured. Progression-free survival (PFS) and overall survival (OS) data will also be collected and analyzed. Assessments will be performed according to standard international criteria. The duration of patient participation will vary by patient depending on clinical benefit and toxicity. Each dose cohort will be analyzed separately for efficacy, safety, and pharmacokinetics (PK).
Study Objectives	**Primary Objective:** To characterize the efficacy of ponatinib administered in 3 starting doses (45 mg, 30 mg, and 15 mg daily) in patients with CP-CML who are resistant to prior TKI therapy or have T315I mutation, as measured by ≤ 1% BCR-ABL1^{IS} at 12 months. **Secondary Objectives:** • To characterize the rate of major molecular response (MMR) at 12 and 24 months and rate of major cytogenetic response (MCyR) by 12 months • To evaluate duration of MMR • To characterize the rates of AOEs, VTEs, AEs, and serious AEs (SAEs) • To evaluate safety differences among the 3 starting dose cohorts, particularly for AOEs and VTEs • To collect sparse PK samples to contribute to population PK and exposure-response analyses of safety and efficacy. **Other Secondary Objectives:** • To characterize the rates of cytogenetic responses and molecular responses; durability will be assessed by evaluating ≤ 1% BCR-ABL1^{IS} response and major molecular response (MMR) at and by 6, 12, 18, and 24 months • To characterize the rate of discontinuation, dose reductions, and interruptions • To characterize the rates of hematologic responses • To evaluate time to response, duration of response, and survival outcomes **Exploratory Objectives:** CCI [redacted]
Study Endpoints	**Primary Endpoint:** ≤ 1% BCR-ABL1^{IS} at 12 months for each starting dose cohort. **Secondary Endpoints:** • Molecular response rates: MMR at 12 and 24 months • Cytogenetic response rates: MCyR by 12 months • Duration of MMR • Safety a. Rate of AOEs and VTEs in each dose cohort b. Rate of AEs in each dose cohort c. Rate of SAEs in each dose cohort

	Other Secondary Endpoints: • Cytogenetic response rates: CCyR at 12 months • Molecular response rates: MR4, and MR4.5 by and at 3-month intervals and MR1 (≤ 10% BCR-ABL1^{IS}) at 3 months • Hematologic response rate: Complete hematologic response (CHR) at 3 months • Tolerability: a. Rate of discontinuation due to AEs in each dose cohort b. Dose reductions due to AE in each dose cohort c. Dose interruptions in each dose cohort • Duration of response: a. Rate of ≤1% BCR-ABL1^{IS} by 12 months and at and by 6, 18, and 24 months b. MMR at and by 6 and 18 months; and by 12 and 24 months • Duration of response in responders • Time to response • Rate of progression to accelerated phase (AP-) or blast phase (BP-) CML • PFS • OS **Exploratory Endpoints:** 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 have received at least two prior TKI therapies and have demonstrated resistance to treatment OR Have documented history of presence of T315I mutation after receiving any number of prior TKI. 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 at screening must demonstrate the BCR-ABL1 fusion by presence of the t(9;22) Philadelphia chromosome i Variant translocations are only allowed provided they meet

inclusion criterion 1d.

c. Resistance to prior TKI therapy is defined as follows (patients must meet at least 1 criterion):

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

ii Six months after the initiation of prior TKI therapy: BCR-ABL1^{IS} >10% and/or Ph+ >65% or new mutation

iii Twelve months after the initiation of prior TKI therapy: BCR-ABL1^{IS} >10% and/or Ph+ >35% or new mutation.

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

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

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

d. > 1% of BCR-ABL1^{IS} as shown by real-time polymerase chain reaction

[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, 1, or 2.

4. Have adequate renal function as defined by the following criterion:

a. Serum creatinine ≤ 1.5 × upper limit of normal (ULN) for institution

b. Estimated creatinine clearance ≥ 30 mL/min (Cockcroft-Gault formula)

5. Have adequate hepatic function as defined by 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 normal QT interval corrected (Frederica) (QTcF) interval on screening electrocardiogram (ECG) evaluation, defined as QTcF of ≤ 450 ms in males or ≤ 470 ms in females.

8. Have a negative pregnancy test documented prior to enrollment (for females of childbearing potential).

9. Agree to use a highly effective form of contraception with sexual partners from randomization through at least 4 months after the end of treatment (for

	female and male patients who are fertile). 10. Provide written informed consent. 11. Be willing and able to comply with scheduled visits and study procedures. 12. Have recovered from toxicities related to prior anticancer therapy to NCI CTCAE v 4.0 grade ≤1.
Main Exclusion Criteria	Patients are not eligible for participation in the study if they meet any of the following exclusion criteria: 1. Have used any approved TKIs or investigational agents within 2 weeks or 6 half-lives of the agent, whichever is longer, prior to receiving study drug. 2. Received interferon, cytarabine or immunotherapy within 14 days; or any other cytotoxic chemotherapy, radiotherapy, or investigational therapy within 28 days prior to receiving the first dose of ponatinib, or have not recovered (> grade 1 by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE], v4.0) from AEs (except alopecia) due to agents previously administered. 3. Have undergone autologous or allogeneic stem cell transplant (SCT) < 60 days prior to receiving the first dose of ponatinib; have any evidence of ongoing graft versus-host disease (GVHD) or GVHD requiring immunosuppressive therapy. 4. Are being considered for hematopoietic SCT (HSCT) within 6-12 months of enrollment (note: ponatinib is not to be used as a bridge to HSCT in this trial). 5. Are taking medications with a known risk of Torsades de Pointes (Appendix A). 6. Have previously been treated with ponatinib. 7. 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. History itself of CNS involvement is not exclusionary if CNS has been cleared with a documented negative lumbar puncture. 8. 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 revascularization procedure, including the placement of a stent d. Congestive heart failure (CHF) (New York Heart Association [NYHA] class III or IV) within 6 months prior to enrollment, or left ventricular ejection fraction (LVEF) less than lower limit of normal, per local institutional standards, within 6 months prior to enrollment e. History of clinically significant (as determined by the treating physician) atrial arrhythmia or any history of ventricular arrhythmia f. Venous thromboembolism, including deep venous thrombosis or pulmonary embolism, within 6 months prior to enrollment 9. Have uncontrolled hypertension (i.e., >150 and >90 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. 10. Have poorly controlled diabetes defined as HbA1c values of > 7.5%. Patients with preexisting, well-controlled, diabetes are not excluded. 11. Have a significant bleeding disorder unrelated to CML. 12. Have a history of alcohol abuse. 13. Have a history of either acute pancreatitis within 1 year of study enrollment or of chronic pancreatitis. 14. Have malabsorption syndrome or other gastrointestinal illness that could affect oral absorption of study drug. 15. Have a history of another malignancy, other than cervical cancer in situ or basal cell or squamous cell carcinoma of the skin; the exception is if patients have been disease-free for at least 5 years and are deemed by the investigator to be at low risk for recurrence of that malignancy. 16. Are pregnant or lactating. 17. Have undergone major surgery (with the exception of minor surgical procedures, such as catheter placement or BM biopsy) within 14 days prior to the first dose of ponatinib. 18. Have an active infection which requires intravenous antibiotics. 19. Have a known history of human immunodeficiency virus infection; testing is not required in the absence of prior documentation or known history. 20. Have any condition or illness that, in the opinion of the investigator, would compromise patient safety or interfere with the evaluation of the drug. 21. Have hypersensitivity to the ponatinib active substance or to any of its inactive ingredients listed in Section 14.7.1.
Approximate Number of Patients	The total enrollment will be 276 patients, with 92 (1:1:1) patients in each cohort.
Approximate Duration of Patient Participation	The duration of patient participation will be approximately 24 months for all patients in the Main Treatment Period, with an option for patients completing or discontinuing from the Main Treatment Period who are still receiving clinical benefit from treatment to enter a Treatment Continuation Period after discussion and agreement between the investigator and medical monitor. Each patient will undergo a period of up to 3 weeks for screening prior to treatment. The duration of therapy will be determined by each patient's response and toxicity profile, and patients may remain on ponatinib in the study if the benefit-risk profile remains favorable. Patients will be followed for 30 days after last dose of study drug.
Approximate Duration of Study	The estimated duration of the trial is at least 60 months, including 36 months for enrollment and 24 months of treatment/follow-up in the Main Treatment Period. The total duration of therapy, and therefore of the study, will be determined by each patient's response and toxicity profile; the study will continue until all patients have been discontinued from the study or the study is terminated by the sponsor (whichever occurs first).

Approximate Number of Study Centers	Approximately 150 centers; multi-national.
Dosage and Administration	Patients will be randomized to receive once-daily oral administration of 1 of 3 starting doses of ponatinib: 45 mg (Cohort A), 30 mg (Cohort B), or 15 mg (Cohort C). Patients starting at 45 mg or 30 mg will have their daily dose reduced to 15 mg upon achievement of ≤ 1% BCR-ABL1^{IS} (as defined within the protocol). Mandatory dose reduction on response details are described in Section 14.1.3. Dose interruptions or reductions should be implemented for patients who experience treatment-related AEs (TRAEs) upon clinical judgment of the investigator. Guidelines for management of TRAEs are described in Section 14.2.2.
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. *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 being treated with ponatinib who have elevated glucose levels. The American Diabetes Association guidelines should be followed, and antidiabetic 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 2003). *Hypertension Treatment* Hypertension (HTN) may contribute to risk of arterial occlusive events. Patients who have HTN should be managed appropriately before initiating treatment. During ponatinib treatment, blood pressure elevations should be monitored and 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). Ponatinib 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. *Prohibited Treatments* The following concurrent medications and treatments are prohibited: • Other anticancer therapies • Other investigational drugs or devices • Medications with a known risk of Torsades de Pointes (see Appendix A) • Herbal preparations or related over-the-counter preparations containing herbal ingredients • Elective surgery requiring inpatient care Medications that are potent inhibitors or inducers of CYP3A4 (see Appendix B)

	should be avoided, but are not prohibited (see Section 14.6). Medications that prolong the QT interval (QT), but are without a known risk of Torsades de Pointes, should be avoided but are not prohibited. If such medications are necessary and are used while a patient is on study, additional ECG monitoring should be performed as clinically indicated.
Efficacy Evaluation	Hematologic response rate, cytogenetic response rate, molecular response rate, and disease progression will be assessed according to standard criteria, as follows: • Bone marrow aspirates for assessment of cytogenetic response • BCR-ABL1^{IS} assessment to determine molecular response • Complete blood count (CBC) for assessment of hematologic response • Survival follow-up Patients will be followed for response, progression, and survival, for 24 months following treatment assignment in the Main Treatment Period. Patients who continue to receive treatment in the Treatment Continuation Period will continue to be followed to ensure continued clinical benefit and compliance with study treatment. Section 12 describes follow-up for all patients in the study.
Safety Evaluation	Safety assessments will include physical and laboratory examinations. AEs will be graded according to the NCI CTCAE, v4.0. All patients receiving at least 1 dose of ponatinib will be considered evaluable for safety. The AE, AOE and VTE incidence rates, as well as the frequency of occurrence of overall toxicity—categorized by toxicity grades (severity)—will be described for each cohort. Listings of laboratory test results will also be generated, and descriptive statistics summarizing the changes in laboratory tests over time will be presented.
Pharmacokinetic Evaluation	Blood samples will be collected at specified time points to characterize the pharmacokinetics of ponatinib. Upon implementation of Amendment 6, no further PK sample collection will be performed as all ongoing patients have completed at least 12 cycles of treatment. Plasma ponatinib concentration-time data will be obtained to contribute to population PK and exposure-response analyses of safety and efficacy. The analysis plan for the population PK and exposure-response analyses will be defined separately and the results of these analyses will be reported separately.
Exploratory Biomarker Evaluation	CCI [redacted]
CCI [redacted]	
Statistical Analysis	**Overview of Trial Design:** This is a phase 2, randomized trial in patients with CP-CML. The study will be

	stratified by age at baseline (≥ 60 vs. < 60 years) and history of hypertension, diabetes, and/or hyperlipidemia (yes/no). Cohorts A, B, and C will consist of CP-CML patients (resistant to previous TKI therapy or who have T315I mutation) being administered a daily starting dose of 45 mg, 30 mg, or 15 mg ponatinib, respectively. Patients starting at 45 mg or 30 mg will have their daily dose reduced to 15 mg upon achievement of ≤ 1% BCR-ABL1^{IS} (as defined below and in the protocol). Each cohort of patients will be analyzed separately for efficacy and safety. The primary endpoint for this trial will be ≤ 1% BCR-ABL1^{IS} rate at 12 months. The primary analysis is planned after all patients have at least 12 months of follow-up; however, preliminary analyses may be performed at earlier time points. Statistical inference will be made for each of the 3 cohorts separately, with the primary endpoint of ≤ 1% BCR-ABL1^{IS} tested at 2-sided 0.05/3=0.0167 significant level using the Bonferroni method for multiplicity adjustment. The primary analysis of the primary endpoint of ≤ 1% BCR-ABL1^{IS} will be performed using a 2-sided exact 98.3% confidence interval (CI) for ≤ 1% BCR-ABL1^{IS} rate based on the intention-to-treat (ITT) population. Any other comparisons will be descriptive. **Sample Size Determination:** The primary endpoint for this trial will be the ≤1% BCR-ABL1^{IS} rate at 12 months. Consistent with the phase 2 PACE trial, the null or uninteresting ≤ 1% BCR-ABL1^{IS} rate is set at 20%. The alternative ≤ 1% BCR-ABL1^{IS} rate is set at 35%. Using the Bonferroni method, the overall 2-sided significant level for statistical testing in each cohort will be set at 0.0167. The primary analysis of the primary endpoint of ≤ 1% BCR-ABL1^{IS} will be performed using a 2-sided exact 98.3% CI for ≤ 1% BCR-ABL1^{IS} rate based on the ITT population. A total sample size of 276 patients or 92 patients in each cohort (1:1:1) will distinguish a favorable ≤ 1% BCR-ABL1^{IS} rate of 35% from a null or an uninteresting ≤ 1% BCR-ABL1^{IS} rate of 20%, with a nominal 80% power and a 1-sided type I error rate of 0.0083 (equivalent to a 2-sided 0.0167) using an exact binomial test. Using the 20% boundary for ≤ 1% BCR-ABL1^{IS}, 29 or more ≤ 1% BCR-ABL1^{IS} responders will be needed for a lower limit of the 2-sided exact 98.3% CI for the ≤ 1% BCR-ABL1^{IS} rate to exceed 20%.
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 (276 patients).

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TABLE OF TABLES

LIST OF APPENDICES

6 LIST OF ABBREVIATIONS

Abbreviation	Term
ABL1	Abelson
ACEI	angiotensin converting enzyme inhibitor
AE	adverse event
AESI	adverse event of special interest
ALL	acute lymphoblastic leukemia/acute lymphocytic leukemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AOEs	arterial occlusive events
AP	accelerated phase
ARB	angiotensin receptor blocker
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-ABL1^{IS}	BCR-ABL1 transcript level as measured by the International Scale
BM	bone marrow
BP	blast phase
BUN	blood urea nitrogen
CAD	coronary artery disease
CBC	complete blood count
CCB	calcium channel blocker
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
CNS	central nervous system
CP	chronic phase
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
cTn	cardiac troponin
CV	cardiovascular
CVEAC	cardiovascular endpoint adjudication committee
CYP	cytochrome P450
DLT	dose-limiting toxicity

Abbreviation	Term
DTP	direct-to-patient
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EMA	European Medicines Agency
CCI	[redacted]
FDA	Food and Drug Administration (United States)
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
GVHD	graft versus-host disease
HBV	Hepatitis B Virus
HDPE	high-density polyethylene
HF	heart failure
CCI	[redacted]
HSCT	hematopoietic stem cell transplantation
HTN	Hypertension
IA	interim analysis
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
IS	international scale
ITT	intention-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LBBB	left bundle branch block
LV	left ventricular
LVEF	left ventricular ejection fraction
MCyR	major cytogenetic response
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labor, and Welfare
MI	myocardial infarction
MMR	major molecular response
MR	molecular response
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute (of the United States)
NYHA	New York Heart Association
OR	odds ratios
OS	overall survival
PCR	polymerase chain reaction

Abbreviation	Term
PCyR	partial cytogenetic response
PFS	progression-free survival
Ph+	Philadelphia chromosome positive
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PRES	posterior reversible encephalopathy syndrome
QD	once daily
CCI	[redacted]
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
QTcF	QT interval corrected (Fridericia)
R/I	resistant or intolerant
SAE	serious adverse event
SAP	statistical analysis plan
SCT	stem cell transplant
SMQ	Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query
SOC	system organ class
SOE	schedule of events
SUSAR	suspected unexpected serious adverse reaction
TdP	Torsades de Pointes
TIA	transient ischemic attack
TKI	tyrosine kinase inhibitor
TLS	tumor lysis syndrome
TRAE	treatment-related AEs
ULN	upper limit of normal
URL	upper reference limit
US/USA	United States of America
VTEs	venous thrombotic/embolic events
WBC	white blood cell

7 DEFINITIONS OF TERMS

Term	Definition
Clinically Significant	A clinical observation or laboratory result that leads to a new intervention or change in therapy is defined in the context of this study as *clinically significant*.
Cycle	For the purposes of this study, a *cycle* consists of 28 days and is equivalent to a month in the measurement of study endpoints.
End-of-Treatment	The *end-of-treatment* occurs at the last dose of study treatment or when the investigator and patient decide that the patient will receive no further study treatment, whichever occurs later.
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 the end of study follow-up period.
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

Term	Definition
	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.
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 drug is ponatinib (investigational medicinal product).
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 open-label study of 3 different starting dosages of ponatinib for treatment of patients with refractory chronic myeloid leukemia (CML) in chronic phase (CP). Ponatinib was designed to inhibit the BCR-ABL1 protein, the pathogenetic driver of CML, with high potency and pan-inhibitory capability. Pan-inhibition refers to ponatinib's ability, in preclinical experiments, to inhibit or prevent the emergence of all single mutations that arise in the course of therapy with imatinib, dasatinib, nilotinib, and bosutinib, and which have been observed to engender resistance of CML to treatment with these currently available tyrosine kinase inhibitors (TKIs). Data from the phase 1 and phase 2 clinical trials of ponatinib have supported the preclinical findings and demonstrated that ponatinib has substantial activity in CML that has become resistant to prior therapy.

Ponatinib (Iclusig®, ARIAD Pharmaceuticals, Inc.) is approved in the United States (US) for the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom no other TKI therapy is indicated and for treatment of adult patients with T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Ph+ ALL. In the European Union (EU), ponatinib is approved for the treatment of adult patients with CML (chronic phase, accelerated phase, or blast phase) and Ph+ ALL who are resistant to dasatinib (or nilotinib for CML) and intolerant to dasatinib (or nilotinib for CML) and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation.

The phase 2 clinical trial of ponatinib in patients with CML or Ph+ ALL who have had prior TKI therapy (AP24534-10-201, PACE), which supported the drug's approvals, tested a starting dose of 45 mg daily. The 5-year data from this study confirmed that treatment with ponatinib continued to provide clinically meaningful responses. In patients with CP-CML, the primary endpoint was met in more than double that of the most recent dasatinib or nilotinib therapy (55.4% vs. 25.8%) and 85.7% remained in the primary endpoint for ≥550 days at 30 mg. The median duration of follow-up was 37.3 months. 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 and venous thrombosis and occlusions—including fatal myocardial infarction (MI), stroke, severe peripheral vascular disease, and the need for urgent revascularization procedures—have been reported in ponatinib-treated patients.

Current data suggest that a dose-effect relationship exists with efficacy and with the occurrence of arterial occlusive events (AOEs), and that a lower daily dose may reduce the incidence of AOEs. This clinical study will assess the relationships of exposure with efficacy and safety: patients will receive a range of initial doses, and at defined time points, patients in response will undergo a dose reduction. The goal of the study will thus be to understand induction of responses, maintenance of responses, safety, and exposure-response as consequences of these dosing strategies.

The primary endpoint of this study will be the achievement of ≤ 1% BCR-ABL1^{IS} at 12 months. This incorporates standard CML approaches to patient care and uses patient monitoring. Increasingly, patient monitoring is being performed by quantitation of BCR-ABL1 transcripts from a standard established by the international scale (IS) (Marin, 2014; NCCN, 2014; Baccarani et al, 2013; Marin et al, 2012; Lauseker et al, 2012; Saglio et al, 2012).

This trial is being conducted in fulfillment of an FDA post-marketing requirement (PMR2113-6).

8.1 Ponatinib Preclinical Summary

In vitro assays demonstrated that ponatinib potently inhibits the kinase enzymatic activity of native ABL1 and mutant versions of the protein, including T315I, with IC_{50} concentrations between 0.4 and 2.0 nM. Ponatinib inhibited the in vitro kinase activity of additional kinases with IC_{50} concentrations between 0.1 and 20 nM, including members of the VEGFR, PDGFR, FGFR, and EPH receptors and the SRC families of kinases, as well as KIT, RET, TIE2, and FLT3. In a cell line expressing native BCR-ABL1, ponatinib inhibited viability with an IC_{50} < 1 nM. Ponatinib also potently inhibited viability (with IC_{50}s < 40 nM) of cell lines expressing 14 major clinically-observed BCR-ABL1 mutants that are resistant to the other approved TKIs. The ability of ponatinib to suppress the emergence of resistant mutants was also assessed. Using an in vitro mutagenesis screen approach, which has successfully predicted mutations that confer clinical resistance to the approved TKIs (Bradeen et al, 2006), 40 nM concentration of ponatinib was found to suppress the emergence of any resistant BCR-ABL1 mutation (O'Hare et al, 2009). Based on these data, the hypothesis that ponatinib will treat BCR-ABL1-driven leukemia with high potency and effectiveness was tested in phase 1, 2, and 3 trials.

8.2 Ponatinib Clinical Efficacy

8.2.1 Phase 1 Clinical Trial of Ponatinib (AP24534-07-101)

The phase 1 trial of ponatinib enrolled 81 patients with hematologic malignancies who had no other effective treatment options. Doses from 2 mg to 60 mg were investigated, and 45 mg was chosen as the recommended phase 2 dose (RP2D). The trial has completed, with all 81 patients discontinued from the study. As of 18 October 2016, the MCyR rate for CP-CML patients (N=31/43) was 72% (CCyR rate of 65.1%) and 83.3% in patients with T315I; the MMR rate for these patients was 55.8%; and the MR4.5 (≤ 0.0032% BCR-ABL1^{IS}) rate was 32.6%. Duration of MCyR ranged from 8 to 345 weeks (median not yet reached), and the Kaplan-Meier method estimated that 72% of responders will remain in MCyR at 4years. At the time of analysis, of the 43 CP-CML patients, 22 who achieved MCyR remained on study—20 of whom were in continuous MCyR.

Steady-state peak plasma concentrations of ponatinib at dose levels of 45 mg, 30 mg, and 15 mg exceeded the concentration (40 nM) required to suppress the emergence of any resistant BCR-ABL1 mutations. Efficacy was demonstrated at each of these dose levels, and responses were maintained for patients who started at 45 mg and reduced to 15 mg (all 3 of the ongoing CP-CML patients in the 15-mg dose cohort had achieved and maintained MCyR at the time of filing).

As of 18 October 2016, the most common treatment-emergent AEs (TEAEs) (≥30%) were rash (49.4 %), nausea (45.7%), fatigue (45.7%), headache (43.2%), arthralgia (39.5%), constipation (39.5%), vomiting (39.5%), hypertension (37.0%), pyrexia (37.0%), edema peripheral (35.8%), platelet count decreased (35.8%), abdominal pain (34.6%), diarrhea (32.1%) and rash erythematous (30.9%).

Overall, 81.5% of patients experienced a treatment-emergent SAE. Pancreatitis, the dose-limiting toxicity (DLT) in the phase 1 study, was the most common treatment-related SAE, occurring in 12.3% of patients. The SAEs with the highest incidence (> 5% of patients), regardless of relationship to study treatment, were febrile neutropenia (14.8%), pneumonia (13.6%), pancreatitis (12.3%), pyrexia (11.1%), neoplasm progression (8.6%), abdominal pain (7.4%), atrial fibrillation (7.4%), and dyspnea (6.2%). Serious AOEs and VTEs occurred in 24 patients (30%): 13 (16%) had cardiovascular SAEs, 5 (6%) had cerebrovascular SAEs, 7 (9%) had peripheral vascular SAEs, and 4 (5%) had venous SAEs. A more detailed presentation of AEs is provided in the Clinical Investigator's Brochure for ponatinib.

8.2.2 Phase 2 Clinical Trial of Ponatinib (AP24534-10-201, PACE)

The phase 2 trial enrolled 449 patients with refractory CML (all phases) or Ph+ ALL that was either resistant or intolerant (R/I) to dasatinib or nilotinib or with the T315I mutation. Patients received 45 mg ponatinib orally once daily (QD). The 5-year study report was completed, with 10 patients still ongoing at 1 site in Korea as of the data cutoff date of 06 February 2017. Median duration of follow-up for the overall population was 37.3 months (range: 0.07-73.13). As of 06 February 2017, the overall MCyR rate for CP-CML patients (N=148) was 55.4% and overall CCyR rate was 46.1% (N=123). The MCyR and CCyR rate for CP-CML R/I patients were 50.7% and 39.9% respectively, and for CP-CML patients with the T315I mutation confirmed at baseline, the MCyR and CCyR rates were 70.3% and 65.6% respectively. The overall MMR rate was 40.4% (57.8% in T315I patients) (Table 1).

Table 1 Best Response to Therapy (Treated Population) in CP-CML Patients (AP24534-10-201)

	CP-CML Patients		
	Total N=267	**Cohort A CP/R/I N=203**	**Cohort B CP/T315I N=64**
Hematologic, n (%)[a]	**N=267**	**N=203**	**N=64**
CHR[a]	251 (94.0)	192 (94.6)	59 (92.2)
Cytogenetic, n (%)[b]	**N=267**	**N=203**	**N=64**
MCyR	148 (55.4)	103 (50.7)	45 (70.3)
CCyR	123 (46.1)	81 (39.9)	42 (65.6)
PCyR	25 (9.4)	22 (10.8)	3 (4.7)
Molecular, n (%)[c]	**N=267**	**N=203**	**N=64**
MMR	108 (40.4)	71 (35.0)	37 (57.8)

Data extraction date: 06 February 2017
[a] Hematologic response is defined as CHR for Cohorts A and B.
[b] Patients entering the study in PCyR must have achieved a CCyR to be considered as having met MCyR criteria.
[c] Patients for whom a valid baseline MMR assessment was missing or who met the criteria for MMR at baseline were analyzed as nonresponders.
Abbreviations: CP-CML=chronic phase chronic myeloid leukemia; CHR=complete hematologic response; MCyR=major cytogenetic response; CCyR=complete cytogenetic response; PCyR=partial cytogenetic response; MMR=major molecular response; R/I=resistant/intolerant

As of 06 February 2017, the most commonly reported TEAEs (i.e., incidence of ≥20% of 449 patients overall, in decreasing order of frequency) were platelet count decreased, abdominal pain, rash, constipation, headache, dry skin, hypertension, fatigue, pyrexia, arthralgia, nausea, neutrophil count decreased, anemia, diarrhea, lipase increased, vomiting, myalgia, and pain in extremity.

SAEs considered to be treatment-related were reported in 172/449 patients (38.3%). The most common SAEs considered by the Investigator to be treatment-related were pancreatitis (25/449 patients; 5.6%) and peripheral arterial occlusive disease (14/449 patients; 3.1%). All other treatment-related SAEs were reported in <3% of the overall population. In general, treatment-related SAEs were reported in a higher proportion of CP-CML patients (who had the longest treatment duration) compared with AP-CML and dBP-CML/Ph+ ALL patients.

8.3 Dose-Response Analyses

This clinical trial will test 2 modulations of dose: both a range of starting doses utilized in the phase 1 and 2 clinical trials (as described in Section 8.2.1 and Section 8.2.2), and dose reduction at defined time points for patients in response. The data that support these approaches derive from univariate and multivariate analyses of the relationship of dose, efficacy, and safety and analyses of the effects of dose reductions on response and safety.

8.3.1 Dose Intensity and Efficacy

The impact of dose on MCyR in patients with CP-CML has been evaluated using 2 methodologies: a multivariate analysis adjusting for covariates, and an analysis of dose response in patients with at least 3 months of follow-up that separates them into tertiles of dose intensity (the latter analysis also includes CCyR and MMR). Both analyses show that increasing

dose intensity is associated with higher response rates, and that factors affecting MCyR rate include dose intensity, patient age, prior TKI exposure, and baseline platelet counts (Table 2).

Table 2 Multivariate Logistic Regression Analyses of MCyR by 12 Months in CP-CML Patients (AP24534-10-201)

	Reduced Multivariate Model[1]		Unit for OR
Covariate	**OR**	**p-value**	
Dose intensity to time of first event	***3.222***	***< 0.0001***	***15 mg/day***
Time Since Diagnosis (years)		NS	10 years
Prior Regimens (up to 6)	0.734	0.0028	1
Baseline T315I Mutation		NS	1
log10 Baseline Neutrophils		NS	1
log10 Baseline Platelets	2.236	0.1207	1
Age (years)	0.808	0.0415	10 years
Number TKIs		NS	1
Medical Hx of Diabetes		NS	1
Medical Hx of Ischemia		NS	1

[1]Data extraction date: 03 September 2013
Abbreviations: Hx=history, NS=not significant, OR=odds ratio.

As further evidence, an analysis of CP-CML patients from the phase 2 PACE trial who had received at least 3 months of follow-up showed a decline in MCyR and MMR from the highest dose-intensity tertile to the lowest dose-intensity tertile (Table 3). Response rates are nevertheless high in the lowest tertile and higher in the higher tertiles.

Table 3 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).
Abbreviations: CCyR=complete cytogenetic response, MCyR=major cytogenetic response, MMR=major molecular response.

In a population with refractory disease and few viable treatment options, achieving an initial response is among the most important goals of TKI treatment. The starting dose of 45 mg once daily used in the phase 2 trial of ponatinib has been shown to yield responses in a high proportion of patients. The exposure-response analyses to date also support the conclusions from univariate and multivariate analyses: that patients who receive a higher starting dose (and therefore, a higher exposure, on average) achieve a response more quickly. However, response rates are sufficiently high to reasonably attempt identification—both prospectively and with greater resolution—of the effect of lower starting doses. Thus, this clinical study will test starting doses across the range of doses (45, 30, and 15 mg) utilized in the phase 2 and phase 3

programs, with an aim to identify with specificity the response rates obtainable with lower initial doses of ponatinib.

8.3.2 Dose Intensity and Safety

Multivariate analyses on data from the phase 2 PACE trial were also performed to elucidate the relationship between dose intensity (as measured by the daily dose given) and safety. In general, increasing dose intensity correlated with an increased probability of experiencing AEs. The factors associated with a lower probability of AEs were younger age, less time since diagnosis, and fewer prior TKIs. Patients with a T315I mutation (who were generally younger, with a shorter time since diagnosis and fewer prior TKI therapies) did, in fact, experience less thrombocytopenia and neutropenia.

With longer follow-up and the accumulation of AOEs and VTEs, the relationship between dose intensity and the 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.

The specific relationships among dose, AOEs and VTEs, and clinical covariates were also examined. Data are shown below in Table 4. The analysis demonstrates that the strongest associations with the occurrence of vascular events were observed with age (odds ratio 1.82; $p < 0.0001$), a medical history of diabetes (odds ratio 3.69; p=0.0003), dose intensity (odds ratio 1.99/15-mg dose; p=0.0009), a medical history of ischemia (odds ratio 2.46; p=0.0087), and time since diagnosis (odds ratio 2.03; p=0.0228). Other contributing factors were baseline neutrophil (p=0.0276) and platelet counts (p=0.0466), the number of prior regimens (p=0.0755), and the presence of the T315I mutation (p=0.1328).

Table 4 Multivariate Logistic Regression Analysis of Arterial Occlusive Events (AP24534-10-201)

	Reduced Multivariate Model	
Covariate	**Odds Ratio[1]**	**p-value**
Dose intensity to time of first event (mg/day)	1.99	0.0009
Time Since Diagnosis (years)	2.03	0.0228
Prior Regimens (up to 6)	0.81	0.0755
Baseline T315I Mutation	1.69	0.1328
log10 Baseline Neutrophils	2.00	0.0276
log10 Baseline Platelets	2.16	0.0466
Age (years)	1.82	< 0.0001
Medical History of Diabetes	3.69	0.0003
Medical History of Ischemia	2.46	0.0087

Data extraction date: 03 September 2013
Includes all phase 2 PACE study patients with baseline data available (N=441).
[1]Odds ratio values below 1 indicate a negative correlation, while values above 1 indicate a positive correlation.

These data suggest that the risk of AOEs can be influenced by dose, as well as by clinical and historical factors pertaining to the patient population. The data, in conjunction with the

dose-response data discussed above, provide the rationale for testing lower starting doses in CP-CML patients. They also suggest that other measures to lower exposure, such as dose reduction, may be protective.

8.4 Rationale for Dose Reduction after Response

Dose intensity appears to be related to the risk of arterial occlusive events, and preliminary analyses in patients with AEs suggest that patients can maintain response on doses lower than 45 mg. The multivariate analysis demonstrates that several covariates contribute significantly to the risk of vascular events.

Data demonstrate that despite reductions in dose intensity (as a result of AEs), patients are able to maintain responses. Data from the patients in the phase 2 PACE trial who underwent dose reduction are shown in Table 5.

Table 5 Summary of Patients who Dose Reduced in AP24534-10-201 by Time Period

	Achieved Response at 45 mg (N=87, 82 maintained response)		Achieved Response at 30 mg (N=46, 41 maintained response)	
Dose Reduction Period	**Number of Patients**	**Maintained Response**	**Number of Patients**	**Maintained Response**
Any Dose Reduction	59	59 (100%)	29	28 (97%)
≥ 60 Day Reduction	48	48 (100%)	20	20 (100%)
≥ 90 Day Reduction	32	32 (100%)	14	14 (100%)
≥ 120 Day Reduction	30	30 (100%)	13	13 (100%)
≥ 180 Day Reduction	27	27 (100%)	12	12 (100%)
≥ 360 Day Reduction	19	19 (100%)	9	9 (100%)
Data extraction date: 06 January 2014				

These findings illustrate that patients who achieved response, either at 45 mg or 30 mg, maintained responses after dose reduction (because of AEs) to 30 mg or 15 mg. The maintenance of response appears to be independent of the length of dose reduction. Thus, there is a rationale for testing a standard approach to dose reduction in patients who have achieved response in this study.

Taken together, these data support the use of a 45-mg dose or a 30-mg dose to achieve a response in patients with no effective treatment options, and to then reduce the dose to maintain response while lowering the risk of long-term AEs.

8.5 Rationale behind Measures to Reduce Risk

Therapy with ponatinib should be initiated by a physician experienced in the diagnosis and treatment of patients with leukemia. As discussed and as demonstrated in the multivariate analyses, several aspects of patient history contribute to the risk of developing vascular complications of therapy; while patients both with and without risk factors experience such complications, the presence of certain risks is strongly associated with AEs. Table 6 demonstrates the univariate relationship between a variety of historical risk factors and the occurrence of vascular complications in the phase 2 PACE trial.

Table 6 Summary of Results of Univariate Logistic Regression Analysis of Arterial SAE Rates in AP24534-10-201

Risk Factor	Arterial SAE Rate in PACE Patients with Risk Factor[1]	Arterial SAE Rate in PACE Patients Excluding Patients with Risk Factor[2]	Relative Risk
None	-	11.8%	
History of MI (n=18)	44.4%	10.4%	4.3
History of CAD (n=33)	42.4%	9.4%	4.5
History of coronary revascularization (n=14)	42.9%	10.8%	4.0
History of ischemic cardiac disease (n=57)	29.8%	9.2%	3.2
History of nonischemic cardiac disease (n=192)	13.5%	10.5%	1.3
History of ischemic disease (n=100)	27.0%	7.4%	3.6
Venous thromboembolism (n=8)	10.5%	11.9%	0.9
Diabetes (n=72)	23.6%	9.5%	2.5
Hypertension (n=239)	18.4%	4.3%	4.3
Hypercholesterolemia (n=246)	15.0%	7.9%	1.9
Obesity (n=109)	12.8%	11.5%	1.1
Age ≥ 65 years (n=155)	16.1%	9.5%	1.7
Any risk factor or disease history (n=376)	13.6%	2.7%	5.0
1 or more risk factors (n=344)	14.0%	4.8%	2.9
2 or more risk factors (n=214)	18.2%	6.0%	3.0
3 or more risk factors (n=88)	21.6%	9.4%	2.3
4 risk factors (n=20)	30.0%	11.0%	2.7

Data extraction date: 03 September 2013
[1]Patients with risk factor who had arterial SAEs/total patients with risk factor in phase 2 PACE study.
[2]Patients without risk factor who had arterial SAEs/total patients without risk factor in phase 2 PACE study.
Abbreviations: CAD=coronary artery disease; MI=myocardial infarction

It is clear that certain risks, such as prior MI or coronary disease, can be discretely identified in patient medical history and are associated with increased risk. Thus, based on these observations, patients with MI, unstable angina, or CHF within 3 months prior to the first dose of ponatinib are excluded from the study. Similarly, patients with a history of clinically significant atrial arrhythmia or any ventricular arrhythmia are also excluded.

Other identified baseline risk factors for serious AOEs and VTEs include diabetes mellitus, hypertension, and hypercholesterolemia. These conditions can be managed in the course of therapy; consequently, their appropriate medical treatment and control are mandatory in this clinical trial.

8.6 Rationale for the Ponatinib Phase 2 Dose-Ranging Clinical Trial

Ponatinib is approved for the treatment of CP-CML patients, based on response rate observations in refractory patients in a phase 2 clinical trial (AP24534-10-201, PACE). Responses were achieved in heavily pretreated patients and in patients who had resistance mutations, but also in patients who did not. Responses were durable, with 39.6% of CP-CML patients continuing to receive clinical benefit and remaining on ponatinib for > 4 years. 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 approvals in the US and EU. Thus, there exists a need to examine strategies to lessen vascular complications of long-term therapy in these patients who have a substantial, unmet therapeutic need and stand to benefit from ponatinib therapy.

Analyses from the phase 1 and phase 2 trials suggest that a dose-effect relationship exists with the occurrence of responses. The conclusions of the multivariate analyses support the proposition that higher dose intensities in refractory patients yield higher response rates across the dose ranges tested. This provides the basis for retaining a starting dose of 45 mg daily, which will maximize the possibility of each patient achieving a rapid response and maintaining it—both key requirements of successful therapy in patients with this unmet medical need. Based on the preclinical findings and additional clinical observations, supporting evidence points to lower dose intensities having the capability to induce and maintain cytogenetic responses in patients with CP-CML. Steady-state peak plasma concentrations of ponatinib at dose levels of 45 mg, 30 mg, and 15 mg exceeded the concentration (40 nM) required to suppress the emergence of any resistant BCR-ABL1 mutations. Efficacy was demonstrated at each of these dose levels, and responses were maintained for patients who started at 45 mg and reduced to 15 mg. Thus, the initial doses in this study will be 45 mg, 30 mg, and 15 mg daily.

The accumulation of vascular complications is also related to dose. Although patients without pre-existing risk factors experience vascular AEs, several risks have been identified that can aid in selecting appropriate patients for therapy; additionally, the management of concurrent medical conditions may further mitigate risk.

In summary, this randomized phase 2 clinical trial will examine a range of ponatinib doses—both initially and as part of a dose reduction strategy—in CP-CML patients, and will generate data on efficacy and safety in relation to dose, supported by pharmacokinetic data. The goal of this study is to test the hypothesis that each of the 3 starting doses will demonstrate the continued efficacy of ponatinib, and that the dose reduction strategy will lessen vascular occlusive complications in the resistant CP-CML patient population—including patients with or without the T315I mutation who have no alternative therapies available.

9 STUDY OBJECTIVES

9.1 Primary Objective

- To characterize the efficacy of ponatinib administered in 3 starting doses (45 mg, 30 mg, and 15 mg daily) in patients with CP-CML who are resistant to prior TKI therapy or have T315I mutation, as measured by ≤ 1% BCR-ABL1^{IS} at 12 months.

9.2 Secondary Objectives

- To characterize the rate of major molecular response (MMR) at 12 and 24 months and rate of major cytogenetic response (MCyR) by 12 months
- To evaluate duration of MMR

- To characterize the rates of AOEs, VTEs, AEs, and SAEs
- To evaluate safety differences among the 3 starting dose cohorts, particularly for AOEs and VTEs
- To collect sparse PK samples to contribute to population PK and exposure-response analyses of safety and efficacy

9.3 Other Secondary Objectives

- To characterize the rates of cytogenetic responses and molecular responses; durability will be assessed by evaluating ≤ 1% BCR-ABL1^{IS} and MMR at and by 6, 12, 18, and 24 months
- To characterize the rates of discontinuation, dose reductions, and dose interruptions
- To characterize the rates of hematologic responses
- To evaluate time to response, duration of response, and survival outcomes

9.4 Exploratory Objectives

CCI

[redacted]

10 INVESTIGATIONAL PLAN

10.1 Overall Study Design and Plan

This is a multi-center, randomized phase 2 trial to characterize the efficacy of ponatinib over a range of 3 starting doses. Eligible patients must have CP-CML; have received at least 2 prior TKI therapies and have demonstrated resistance to treatment or have the T315I mutation, as defined in Section 11. The trial will also assess the short- and long-term safety of the 3 starting doses investigated.

Patients will be randomized to receive once-daily oral administration of 1 of 3 starting doses of ponatinib: 45 mg (Cohort A), 30 mg (Cohort B), or 15 mg (Cohort C). Patients starting at 45 mg or 30 mg will have their daily dose reduced to 15 mg upon achievement of ≤ 1% BCR-ABL1^{IS}, as described in Section 14.1.3. In the event of loss of ≤ 1% BCR-ABL1^{IS} after dose reduction for response, and in the absence of AEs necessitating continued dose reduction, escalation back to the starting dose will be allowed, upon review and agreement with the medical monitor.

All randomized patients will enter the Main Treatment Period. Patients will remain on treatment in the Main Treatment Period for 24 months. Following completion of or withdrawal from the Main Treatment Period (as described in Section 12.4.1), patients who are both tolerating treatment and receiving clinical benefit from treatment may enter into the optional Treatment Continuation Period upon discussion and agreement between the investigator and medical monitor. Examples of clinical benefit that could allow a patient to enter the Treatment Continuation Period include (but are not limited to) a reduction from baseline in BCR-ABL^{IS} levels (but without meeting the protocol-defined response criterion of ≤ 1% BCR-ABL1^{IS} at 12 months), an improvement in hematologic parameters (but without meeting the

protocol-defined response criterion of complete hematologic response [CHR] by 3 months), or a BCR-ABL^{IS} level indicative of clinical benefit (but that is > 1%, after loss of ≤ 1% BCR-ABL1^{IS} at an earlier time point; see Section 12.4.1.1). Each patient may remain on study treatment during the Treatment Continuation Period until the patient either stops receiving clinical benefit or experiences unacceptable toxicity, or until the study is terminated by the sponsor (whichever occurs first). Section 12 describes follow-up and data collection for patients in each of the Main Treatment and Treatment Continuation Periods.

The trial will assess hematologic response, cytogenetic response, and molecular response, as well as characteristics of efficacy including time and duration of responses, both by starting dose and after dose reduction. AE rates—and the rates, in particular, of arterial occlusive events—will be summarized. PFS and OS data will also be collected and analyzed. Assessments will be performed according to standard international criteria. Each dose cohort will be analyzed separately for efficacy, safety, and PK parameters.

10.1.1 Primary Endpoint

- ≤ 1% BCR-ABL1^{IS} at 12 months for each dose cohort

10.1.2 Secondary Endpoints

- Molecular response rates: MMR at 12 and 24 months
- Cytogenetic response rates: MCyR by 12 months
- Duration of MMR
- Safety
    a. Rate of AOEs and VTEs in each dose cohort
    b. Rate of AEs in each dose cohort
    c. Rate of SAEs in each dose cohort

10.1.3 Other Secondary Endpoints

- Cytogenetic response rates: CCyR at 12 months
- Molecular response rates: MR4, and MR4.5 by and at 3-month intervals and MR1 (≤ 10% BCR-ABL1^{IS}) at 3 months
- Hematologic response rate: CHR at 3 months
- Tolerability:
    a. Rate of discontinuation due to AEs in each dose cohort
    b. Dose reductions due to AE in each dose cohort
    c. Dose interruptions in each dose cohort

- Duration of response:
  a. Rates of ≤ 1% BCR-ABL1^{IS} by 12 months and at and by 6, 18, and 24 months
  b. MMR at and by 6 and 18 months; and by 12 and 24 months
- Duration of response in responders
- Time to response
- Rate of progression to AP- or BP-CML
- PFS
- OS

10.1.4 Exploratory Endpoints

CCI

[redacted]

10.2 Description of Treatment

Patients will be randomized to receive once-daily oral administration of 1 of 3 starting doses of ponatinib: 45 mg (Cohort A), 30 mg (Cohort B), or 15 mg (Cohort C).

Mandatory dose reduction: Patients will undergo assessments for achievement of ≤1% BCR-ABL1^{IS} and for consideration of mandatory dose reduction at 3, 6, 9, and 12 months (or if an unscheduled response assessment is performed). The schedule for dose reduction is described in Section 14.1.3.

Escalation for loss of response following dose reduction: Patients who undergo dose reduction upon achievement of ≤ 1% BCR-ABL1^{IS} and who, with continued monitoring, lose the ≤ 1% BCR-ABL1^{IS} may undergo dose escalation back to the starting dose at the discretion of the physician and upon review with the medical monitor. The dose re-escalation schema is described in Section 14.1.4.

Dosing during the Treatment Continuation Period: Patients in the Treatment Continuation Period will be treated with study drug in accordance with Section 14.1.5.

10.3 Randomization

Patients will be randomized in a 1:1:1 ratio to receive ponatinib in one of three different starting dose cohorts:

- Cohort A: 45 mg QD with reduction to 15 mg at 3, 6, 9, or 12 months upon achievement of ≤ 1% BCR-ABL1^{IS}
- Cohort B: 30 mg QD with reduction to 15 mg at 3, 6, 9, or 12 months upon achievement of ≤ 1% BCR-ABL1^{IS}
- Cohort C: 15 mg QD with no change upon achievement of ≤ 1% BCR-ABL1^{IS}

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

The randomization will be stratified based on the patient's baseline age (≥ 60 vs < 60 years) and history of hypertension, diabetes, and/or hyperlipidemia (yes/no). Specific instructions for randomization will be supplied in the Study Reference Manual. Randomization procedures should be performed following complete eligibility assessments and prior to the initiation of assigned treatment. This study is open-label; patients, investigators, and the sponsor will know the identity of each patient's study treatment.

10.4 Treatment Periods

For each patient, treatment will start with the Main Treatment Period. Following completion of the 24-month Main Treatment Period or following early withdrawal from the Main Treatment Period before completing all 24 cycles of the Main Treatment Period (as described in Section 12.4.1), patients who are both tolerating ponatinib treatment and receiving clinical benefit from treatment may enter into an optional Treatment Continuation Period upon discussion and agreement between the investigator and medical monitor.

10.4.1 Main Treatment Period

Patients will be treated with their randomized dose of study drug, with mandatory dose reduction and the option for dose re-escalation for loss of response, as described in Section 10.2. Patients will remain in the Main Treatment Period until meeting any of the criteria for withdrawal (see Section 12.4.1), or until completing the full 24 cycles of the Main Treatment Period.

10.4.2 Optional Treatment Continuation Period

Patients who either complete the 24-cycle Main Treatment Period or who discontinue before completing 24 cycles because of failure to achieve or maintain protocol-defined responses (see Section 12.4.1.1) may enter the Treatment Continuation Period on a case-by-case basis if they are both tolerating treatment and receiving clinical benefit from ponatinib administration as determined by agreement between the investigator and medical monitor. Written permission from the medical monitor must be obtained in advance of each patient entering the Treatment Continuation Period. Patients who enter the Treatment Continuation Period will be evaluated as per the SOE shown in Table 8. For patients in the Treatment Continuation Period, the follow-up schedule will be arranged so that contact between the patient and the site occurs at least once every 3 months and a study visit occurs at least once every 6 months. Objective evidence supporting such continuation treatment will include overall tolerance, hematologic evidence for disease control relative to baseline, and lack of events requiring study discontinuation (Section 12.4.2).

With continued agreement between the investigator and medical monitor, each patient in the Treatment Continuation Period may remain on ponatinib until the patient stops receiving clinical benefit or experiences unacceptable toxicity, or until the study is terminated by the sponsor (whichever occurs first). The clinical benefit to the patient must be assessed by the investigator and medical monitor, with key evidence supporting clinical benefit recorded in the source documents, and with study-specific clinical data recorded both in the source documents and in the electronic case report form (eCRF).

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 7. Documentation from the screening period is required for each inclusion and exclusion criterion.

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

1. Have CP-CML and have received at least two prior TKI therapies and have demonstrated resistance to treatment

   OR

   Have documented history of presence of T315I mutation after receiving any number of prior TKI.

   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 $\geq 100 \times 10^9$/L platelets ($\geq 100{,}000/mm^3$)

      v No evidence of extramedullary disease except hepatosplenomegaly

      vi No prior diagnosis of AP- or BP-CML

   b. Cytogenetic assessment at screening must demonstrate the BCR-ABL1 fusion by presence of the t(9;22) Philadelphia chromosome.

      i Variant translocations are only allowed provided they meet inclusion criterion 1d.

   c. Resistance to prior TKI therapy is defined as follows (patients must meet at least 1 criterion):

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

      ii Six months after the initiation of prior TKI therapy: BCR-ABL1^{IS} >10% and/or Ph+ >65% or new mutation

      iii Twelve months after the initiation of prior TKI therapy: BCR-ABL1^{IS} >10% and/or Ph+ >35% or new mutation

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

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

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

d. >1% BCR-ABL1^{IS} as shown by real-time polymerase chain reaction

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

2. Age ≥ 18 years old.
3. Have an ECOG performance status of 0, 1, or 2.
4. Have adequate renal function as defined by the following criterion:
   a. Serum creatinine ≤ 1.5 × ULN for institution
   b. Estimated creatinine clearance ≥ 30 mL/min (Cockcroft-Gault formula)
5. Have adequate hepatic function as defined by the following criteria:
   a. Total serum bilirubin ≤ 1.5 × ULN, unless due to Gilbert's syndrome
   b. ALT ≤ 2.5 × ULN, or ≤ 5 × ULN if leukemic infiltration of the liver is present
   c. 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 normal QTcF interval on screening ECG evaluation, defined as QTcF of ≤ 450 ms in males or ≤ 470 ms in females.
8. Have a negative pregnancy test documented prior to enrollment (for females of childbearing potential).
9. Agree to use a highly effective form of contraception with sexual partners from randomization through at least 4 months after the end of treatment (for female and male patients who are fertile).
10. Provide written informed consent.
11. Be willing and able to comply with scheduled visits and study procedures.
12. Have recovered from toxicities related to prior anticancer therapy to NCI CTCAE v 4.0 grade ≤1.

11.2 Exclusion Criteria

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

1. Have used any approved TKIs or investigational agents within 2 weeks or 6 half-lives of the agent, whichever is longer, prior to receiving study drug.

2. Received interferon, cytarabine or immunotherapy within 14 days, or any other cytotoxic chemotherapy, radiotherapy, or investigational therapy within 28 days prior to receiving the first dose of ponatinib, or have not recovered (> grade 1 by NCI CTCAE, v4.0) from AEs (except alopecia), due to agents previously administered.
3. Have undergone autologous or allogeneic SCT < 60 days prior to receiving the first dose of ponatinib; have any evidence of ongoing GVHD or GVHD requiring immunosuppressive therapy.
4. Are being considered for HSCT within 6-12 months of enrollment (note: ponatinib is not to be used as a bridge to HSCT in this trial).
5. Are taking medications with a known risk of Torsades de Pointes (Appendix A).
6. Have previously been treated with ponatinib.
7. Have active CNS disease as evidenced by cytology or pathology; in the absence of clinical CNS disease, lumbar puncture is not required. History itself of CNS involvement is not exclusionary if CNS has been cleared with a documented negative lumbar puncture.
8. Have clinically significant, uncontrolled, or active cardiovascular disease, specifically including, but not restricted to:
    a. Any history of MI, unstable angina, cerebrovascular accident, or TIA
    b. Any history of peripheral vascular infarction, including visceral infarction
    c. Any revascularization procedure, including the placement of a stent
    d. Congestive heart failure (CHF) (New York Heart Association [NYHA] class III or IV) within 6 months prior to enrollment, or left ventricular ejection fraction (LVEF) less than lower limit of normal, per local institutional standards, within 6 months prior to enrollment
    e. History of clinically significant (as determined by the treating physician) atrial arrhythmia or any history of ventricular arrhythmia
    f. Venous thromboembolism, including deep venous thrombosis or pulmonary embolism, within 6 months prior to enrollment
9. Have uncontrolled hypertension (i.e., >150 and >90 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.
10. Have poorly controlled diabetes defined as HbA1c values of > 7.5%. Patients with preexisting, well-controlled, diabetes are not excluded.
11. Have a significant bleeding disorder unrelated to CML.
12. Have a history of alcohol abuse.
13. Have a history of either acute pancreatitis within 1 year of study enrollment or of chronic pancreatitis.

14. Have malabsorption syndrome or other gastrointestinal illness that could affect oral absorption of study drug.
15. Have a history of another malignancy, other than cervical cancer in situ or basal cell or squamous cell carcinoma of the skin; the exception is if patients have been disease-free for at least 5 years, and are deemed by the investigator to be at low risk for recurrence of that malignancy.
16. Are pregnant or lactating.
17. Have undergone major surgery (with the exception of minor surgical procedures, such as catheter placement or BM biopsy) within 14 days prior to first dose of ponatinib.
18. Have an active infection which requires intravenous antibiotics.
19. Have a known history of human immunodeficiency virus infection; testing is not required in the absence of prior documentation or known history.
20. Have any condition or illness that, in the opinion of the investigator, would compromise patient safety or interfere with the evaluation of the drug.
21. Have hypersensitivity to the ponatinib active substance or to any of its inactive ingredients listed in Section 14.7.1.

12 STUDY PROCEDURES

12.1 Schedule of Events

Table 7 lists the screening and study procedures to be performed through Cycle 12. Table 8 lists the procedures to be performed after Cycle 12 through the end 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 trial. 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 performed within 21 days prior to randomization, with the exception of the screening bone marrow (BM) aspirate (to be performed within 42 days) and screening pregnancy test (to be performed within 7 days of first dose of study 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 trial begins with the signing and dating of the informed consent form.

3 Randomization

Specific instructions for randomization will be supplied in the Study Reference Manual. Randomization procedures should be performed within the 21-day screening period, following complete 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 include diagnoses, therapies, and medical and surgical treatments.

Special attention should be paid to documenting risk factors for cardiovascular, cerebrovascular, peripheral vascular, and venous thromboembolic disease. The history must also include any history of ischemic heart disease (such as 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 TIAs, cerebral atherosclerosis, or revascularization procedures); diabetes mellitus; hypertension; hypercholesterolemia; hyperlipidemia; deep venous thrombosis; pulmonary embolism; any other coagulopathy (for example, protein S or protein C deficiency or anticardiolipin antibody); physical inactivity; obesity; or smoking. Family medical history will be collected, and should include any history of coronary artery disease, early death from myocardial infarction or cerebrovascular accident, sudden death, or 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 those 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, as well as the reason for failure of or intolerance to each regimen. Stem cell transplant or experimental therapy history is also recorded.

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 Physical Examination 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 on Day 28 of every sixth cycle thereafter for patients continuing on to the Treatment Continuation Period, as indicated in Table 7 and Table 8) 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.

10 Complete Blood Count (CBC) with Differential

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—including basophils, myelocytes, metamyelocytes, promyelocytes, and blasts, when present—must be quantified. Hematologic assessments must be obtained at screening and at every subsequent assessment, as specified in the Schedule of Events (Table 7 and Table 8), or more frequently as clinically indicated (e.g., to confirm the 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 7 and Table 8), or more frequently as clinically indicated.

b. Cholesterol/Lipid Assessment

Fasting serum lipid panel (total, high-density lipoprotein [HDL], and low-density lipoprotein [LDL])—including triglycerides—must be collected during screening and at subsequent time points as specified in the Schedule of Events (Table 7 and Table 8), or more frequently as clinically indicated.

c. 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) assessments must be performed at screening. If the investigational site is unable to perform NT-proBNP testing, a BNP test can be performed instead. Additionally, HbA1c, CRP, cTn, and NT-proBNP (or BNP) assessments must be performed at the times specified in the Schedule of Events (Table 7 and Table 8), or more frequently as clinically indicated.

d. 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. Patients who are chronic carriers of Hepatitis B virus (HBV) and receive a BCR-ABL TKI therapy may have a reactivation of Hepatitis B. For patients with evidence of prior or current HBV infection, please refer to the IB version 8, Section 8.1.2.9.

12 Pregnancy Test

The pregnancy test must be a beta-human chorionic gonadotropin (β-HCG) test, using either urine or serum. 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. If the test is deemed necessary, it 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 (ECG)

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 at Cycles 3, 6, 12, 18, 24, and at the end of every sixth cycle thereafter for patients continuing on to the Treatment Continuation Period; and at End-of-Treatment, as specified in the Schedule of Events (Table 7 and Table 8)—or more frequently if clinically indicated. If medications known to prolong the QTcF interval are used while a patient is on study, then additional ECG monitoring should be performed as clinically indicated.

14 Echocardiogram (ECHO)

An ECHO for assessment of LVEF must be performed within the 21-day screening window and at Cycles 12, 24, and at the end of every 12th cycle thereafter for patients continuing on to the Treatment Continuation Period; as well as at End-of-Treatment, as specified in the Schedule of Events (Table 7 and Table 8). Additional ECHOs need only be

performed if clinically indicated.

15 Adverse Events and Concomitant Medications

AEs and concomitant medications are to be recorded continuously throughout the treatment period—starting on the date of signed informed consent—and at the 30-day follow-up visit, as indicated in the Schedule of Events (Table 7 and Table 8). It is expected that new and updated AEs and concomitant medications reported within the treatment period; ongoing AEs thought to be at least possibly study-drug related; and all ongoing SAEs should be followed at least every 4 weeks until they resolve to baseline (or to NCI CTCAE, v4.0 grade ≤ 1), stabilize, or are considered to be chronic/irreversible.

16 Bone Marrow Aspirate/Cytogenetics

The bone marrow (BM) aspirate results should include the components required for assessing response of the patient. All BM aspirates should quantify cell types required for diagnosis and response assessment, including promyelocytes and blasts. Examination should include cytogenetic assessment by conventional banding. Interphase fluorescence in situ hybridization (FISH) is not allowed.

The BM aspirate with or without an optional biopsy 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 is required in all patients on study after the first 12 cycles.

Patients with variant BCR-ABL1 translocations must be assessed for cytogenetic response, utilizing conventional BM cytogenetic techniques, at each time point.

During Cycle 12, all patients must undergo a BM aspirate and cytogenetic assessment.

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 (i.e., 10-fold) increase in transcript level; the exception is if the level remains ≤ 1% BCR-ABL1^{IS}. Bone marrow aspirates and cytogenetic assessments may be performed at other times when clinically indicated (e.g., 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).

17 Blood Samples for BCR-ABL1^{IS} Molecular Response Assessment

Testing of peripheral blood in all patients by quantitative, real-time polymerase chain reaction (PCR) of the BCR-ABL1 transcript must be done at screening; at the end of Cycles 3, 6, 9, 12, 15, 18, 21, and 24; at the end of every 3 cycles thereafter for patients in the Treatment Continuation Period who have completed < 24 total cycles of treatment in the study; at the end of every 6 cycles thereafter (at a minimum) for patients in the Treatment Continuation Period who have completed ≥ 24 total cycles of treatment in the study; and at the End-of-Treatment Visit. Specific instructions will be supplied in the Study Reference Manual.

This test will be performed by a central molecular diagnostics laboratory, and the results will be reported to the participating investigator. However, in cases where a patient's visit to the site is not feasible due to extenuating circumstances, such as the COVID-19 pandemic, evaluation via local laboratories will be permitted. The ratio of BCR-ABL1 to ABL1 transcripts will be reported on the International Scale. For patients with variants of BCR-ABL1 for which there is no International Scale, only the absolute ratio of BCR-ABL1 to ABL1 transcripts will be reported. CCI

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Pharmacokinetic (PK) Samples

A pre-dose blood sample will be collected within 1 hour prior to dosing on Day 28 of Cycles 1, 3, 6, 9 and 12. Samples will also be collected at 1 (± 15 minutes), 4 (± 30 minutes), and 6 (± 30 minutes) hours post-dose on Day 28 in Cycle 1. Additionally, an unscheduled trough assessment (to be collected within 1 hour prior to dosing) will be performed at the first scheduled visit following a dose reduction of at least 7 days' duration prior to the visit.

Patients must be instructed not to take the day's dose of ponatinib until after the pre-dose sample is collected. The pre-dose sample should be collected as close as possible to 24 hours after the prior dose; the administration time of the prior dose must be recorded,

along with the time of the pre-dose PK sample. A[CCI] [redacted]

Upon implementation of Amendment 6, no further PK sample collection will be performed as all ongoing patients have completed at least 12 cycles of treatment.

22 Review of Patient Daily Dosing Diary

The patient dosing diary card will be completed by the patient on a daily basis and reviewed by site staff at each visit.

23 Treatment Continuation Procedures

Continuation patients (including both those who enter the Treatment Continuation Period before completing all 24 cycles of the Main Treatment Period and those who enter the Treatment Continuation Period after completing all 24 cycles of the Main Treatment Period) will generally be evaluated every 3 months according to the schedule of events for the Treatment Continuation Period as shown in Table 8. Upon agreement between the investigator and the medical monitor, patients who have completed ≥ 24 cycles of treatment may be evaluated using an alternating schedule of telephone contact and patient visits (for visits that would otherwise occur at the end of odd- and even-numbered cycles, respectively, as shown in Table 8). In all cases, the schedule will be arranged so that contact between the patient and the site occurs at least once every 3 months and a study visit occurs at least once every 6 months.

Key evidence supporting clinical benefit must be recorded by the investigator in the source documents, with study-specific clinical data recorded both in the source documents and in the eCRF as instructed in the eCRF Completion Guidelines. Patients must be withdrawn from the Treatment Continuation Period if they are no longer receiving clinical benefit in the opinion of the investigator or if they meet any of the criteria shown in Section 12.4.2. The investigator may contact the medical monitor if needed to discuss a patient's continued participation in the Treatment Continuation Period.

24 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 occurs 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. Patients that do not return to the clinic and attempts to contact these patients have been unsuccessful will be considered as lost to follow-up. At least three attempts must be made to contact the patient, and must be documented. See Section 12.2.2 for further details on discontinuation of patients from study drug. For patients continuing on to the optional Treatment Continuation Period, the End-of-Treatment and subsequent follow-up visits should be performed only after the patient discontinues from the optional Treatment Continuation Period.

25 Follow-up Procedures: Safety

All AEs ongoing or starting within 30 days after End-of-Treatment must be recorded on the eCRF. After this time, all ongoing SAEs should be followed at least every 4 weeks until they resolve to baseline (or to NCI CTCAE, v4.0 grade ≤ 1), stabilize, or are considered to be chronic/irreversible.

26 Follow-up Procedures: Survival

Survival data will be collected every 12 weeks ± 14 days, starting after the last dose of ponatinib 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.

Tests and procedures should be performed on schedule, but occasional changes may be allowed for holidays, vacation, and other administrative reasons. If the study schedule is shifted, both assessments and dosing must be shifted to ensure collection of assessment is completed prior to dosing. If extenuating circumstances (such as the COVID-19 pandemic) prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the sponsor/designee medical monitor. Similarly, if extenuating circumstances prevent completion of a scheduled evaluation but an acceptable alternative test can be performed, the patient may continue the study only with written permission of the sponsor/designee medical monitor. Missed or delayed study visits and/or procedures should be recorded as protocol deviations.

12.1.1 Changes to Study Procedures Due to COVID-19 Pandemic

The following information provides guidance regarding changes to the study procedures that could be implemented for study participants or study sites that are affected by the COVID-19 Public Health Emergency. This guidance takes references from the FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency - Guidance for Industry, Investigators, and Institutional Review Boards, March 2020, updated 02 July 2020, and the EMA Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic, Version 3 (28 April 2020).

As the COVID-19 pandemic may peak in different regions at different times and restrictions implemented by local laws and recommendations may vary, any decision on procedural changes should be made on a case-by-case basis by the principal investigator in consultation with the study team and the medical team as needed, while maintaining patient safety and confidentiality as the priority.

Procedural changes due to COVID-19 may include the following:

- All attempts should be made to perform the assessments with the patient present at the site. However, in cases where a patient's visit to the site is not feasible (patient cannot travel to the site, the site is temporarily closed for visits, or in cases where the investigator believes that is best for patient's and site staff's safety not to visit to the site), alternative evaluation such as local laboratories and/or TeleHealth (the ability to connect a physician to a patient)/Telemedicine (remote clinical assessments) or home healthcare

(performing some assessments in a patient's home by a qualified healthcare provider) will be allowed if permitted by local regulations.

  - For home healthcare visits, collection of clinical laboratory samples (blood specimen collection or other diagnostic tests) or ECGs may be performed by the investigator or qualified healthcare professional who can visit the study participant's residence.
  - Remote visits via virtual communications (eg, TeleHealth application) may be performed as a safety check on patient well-being and to verify correct study drug dosing.

- Deviations from the protocol-specified procedures (eg, not collecting a protocol-specified specimen, such as postdose bloodwork) will be recorded as related to COVID-19.
- Missed clinic visits or subject withdrawals due to COVID-19 must be recorded on the eCRF (Section 12.4).
- Allow the use of alternate means to capture patient-reported outcome/QoL data (eg, a paper-based questionnaire mailed to patients) as a back-up only if patients cannot come at site for scheduled visit.
- Allow transfer of study participants to investigational sites away from risk zones or closer to their home to sites already participating in the study or new ones.
- Alternate study drug delivery mechanisms, eg, dispensing additional study drug at clinic visits or direct-to-patient (DTP) delivery of the study drug from the investigational site to patients in compliance with national laws or temporary national emergency measures (Section 14.7.2).

Table 7 Schedule of Events through Cycle 12

Cycle	Screening/ Baseline	Main Treatment Period									
		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
Cycle Day Window	N/A	N/A	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3
Informed Consent[2]	X										
Randomization[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[11]	X	X	X	X	X[a]	X	X[a]	X	X	X	X
Fasting Cholesterol/Lipid Assessment[11]	X			X				X	X	X	X
HbA1c, CRP, Troponin, and NT-proBNP or BNP[11]	X			X				X	X	X	X
Hepatitis B Serology[11]	X										
Pregnancy Test[12]	X										
12-Lead Electrocardiogram[13]	X							X	X		X
Echocardiogram[14]	X										X
Adverse Events[15]	THROUGHOUT TREATMENT PERIOD										
Concomitant Medications[15]	THROUGHOUT TREATMENT PERIOD										
Bone Marrow Aspirate and Cytogenetics[16]	X										X
Blood Sample for Molecular Response Assessment[17]	X							X	X	X	X
CCI [redacted]											
PK Sample[21]				X				X	X	X	X
Review of patient daily dosing diary[22]		X	X	X	X	X	X	X	X	X	X

For footnotes, see Section 12.1.
Definitions: BCR-ABL1= Breakpoint Cluster Region-Abelson; BNP=brain natriuretic peptide; CRP=C-reactive protein; ECOG=Eastern Cooperative Oncology Group; CCI [redacted] =hemoglobin A1c; NT-proBNP=N-terminal pro-brain natriuretic peptide; PK=pharmacokinetic.
a Indicates lipase only assessments.

Table 8 Schedule of Events after Cycle 12 and for the Treatment Continuation Period, End-of-Treatment Visit, and Survival Follow-up

Cycle	Main Treatment Period				Treatment Continuation Period		End-of-Treatment Visit[24]	30-Day Follow-Up Visit[24]	Survival Follow-up[26]
	Cycle 15	Cycle 18	Cycle 21	Cycle 24	Every 3 Months[23]				
					Odd Cycles	Even Cycles			
Day within Cycle	**28**	**28**	**28**	**28**	**28**	**28**	**N/A**	**N/A**	**N/A**
Cycle Day Window	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**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 PERIOD AS CLINICALLY INDICATED								
Complete Blood Count with Differential[10]		X		X		X	X	X	
Chemistry[11]		X		X		X	X	X	
Fasting Cholesterol/Lipid Assessment[11]		X		X		X	X		
HbA1c, CRP, Troponin, and NT-proBNP or BNP[11]		X		X		X	X		
Pregnancy Test[12]							X		
12-Lead Electrocardiogram[13]		X		X		X	X		
Echocardiogram[14]				X		X (at 12-cycle intervals)	X		
Adverse Events[15]	THROUGHOUT TREATMENT PERIOD							X[25]	
Concomitant Medications[15]	THROUGHOUT TREATMENT PERIOD							X	
Bone Marrow Aspirate and Cytogenetics[16]							X		
Blood Sample for Molecular Response Assessment[17]	X	X	X	X	X	X	X		
CCI									
CCI									
CCI									
Review of patient dosing diary[22]	X	X	X	X	X	X	X		
Survival[26]									X

For footnotes, see Section 12.1.
Definitions: BNP=brain natriuretic peptide; CRP=C-reactive protein; ECOG=Eastern Cooperative Oncology Group; CCI ; 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 eligible criteria may be enrolled into the study using the enrollment procedure established by the sponsor. At the time of enrollment, 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 criteria and/or meet the exclusion criteria are defined as screen failures. 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 7) 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 randomized.

If a patient is discontinued from the trial 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

Total study duration is expected to be at least 60 months. This includes an enrollment period of approximately 36 months and a duration of treatment with study drug of 24 months in the Main Treatment Period, unless the patient is discontinued early. Following completion of the 24-month Main Treatment Period or following early withdrawal from the Main Treatment Period before completing all 24 cycles of the Main Treatment Period and upon discussion and agreement with the medical monitor, patients who are receiving clinical benefit from and tolerating Ponatinib may continue to receive treatment in the optional Treatment Continuation Period. The study will continue until all patients have been discontinued from the study or the study is terminated by the sponsor, whichever comes first. Patients will be followed for 30 days after last dose of study drug.

12.4 Withdrawal Criteria

12.4.1 Main Treatment Period

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

- Intolerable toxicity as determined by the investigator and defined in Section 14.2.2
- MI, 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 (see Section 12.4.1.1)
- Absence of MCyR at 12 months (see Section 12.4.1.1)
- Absence of ≤ 1% BCR-ABL1^{IS} at 12 months (see Section 12.4.1.1)
- Loss of ≤ 1% BCR-ABL1^{IS} in the absence of dose re-escalation or continued loss of ≤ 1% BCR-ABL1^{IS}, as defined in Section 16.5.1.1, after 6 months following dose re-escalation (see Section 12.4.1.1)
- Progression of disease to AP- or BP-CML
- Entry into another therapeutic clinical trial (e.g., a trial for another investigational product, a ponatinib rollover study initiated by the sponsor, etc.) 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, including withdrawal related to COVID-19
- Lost to follow-up
- Termination of the trial by the sponsor
- Any other reason that, in the opinion of the investigator, would justify removal of the patient from the study

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

12.4.1.1 Failure to Meet or Maintain Protocol-Defined Response Criteria in the Main Treatment Period

Patients meeting any of the following criteria (requiring discontinuation from the Main Treatment Period; see Section 12.4.1) but who are otherwise receiving clinical benefit from treatment may enter the optional Treatment Continuation Period upon agreement between the investigator and the medical monitor in accordance with Section 10.4.2:

- Absence of CHR by 3 months
- Absence of MCyR at 12 months
- Absence of ≤ 1% BCR-ABL1^{IS} at 12 months
- Loss of ≤ 1% BCR-ABL1^{IS} in the absence of dose re-escalation or continued loss of ≤ 1% BCR-ABL1^{IS}, as defined in Section 16.5.1.1, after 6 months following dose re-escalation

These continuation patients will be followed according to the schedule described in Section 12.1.

12.4.2 Treatment Continuation Period

Patients in the Treatment Continuation Period will be followed according to the schedule described in Section 12.1. Patients must be discontinued from further study drug administration in the Treatment Continuation Period if any of the following occur:

- Intolerable toxicity as determined by the investigator and/or medical monitor
- MI, unstable angina, stroke, TIA, or urgent revascularization
- A treatment interruption for study-drug related nonhematologic toxicities lasting longer than 28 days
- Progression of disease to AP- or BP-CML
- Entry into another therapeutic clinical trial (e.g., a trial for another investigational product, a ponatinib rollover study initiated by the sponsor, etc.) 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, including withdrawal related to COVID-19
- Lost to follow-up
- Termination of the trial by the sponsor
- Any other reason that, in the opinion of the investigator, would justify removal of the patient from the study

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

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:

- BM aspirates for assessment of cytogenetic response
- BCR-ABL1^{IS} assessment to determine molecular 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 CTCAE, v4.0), 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 PK Evaluations

Plasma ponatinib concentration-time data will be obtained to contribute to population PK and exposure-response analyses of safety and efficacy. The analysis plan for the population PK and exposure-response analyses will be defined separately and the results of these analyses will be reported separately.

Upon implementation of Amendment 6, no further PK sample collection will be performed as all ongoing patients have completed at least 12 cycles of treatment.

CCI

[redacted]

CCI

14 STUDY TREATMENT

14.1 Study Treatment

Patients will be randomized to receive ponatinib at 1 of 3 starting doses (45 mg, 30 mg, or 15 mg) QD. Ponatinib will be self-administered by the patient on a daily schedule. Each 28-day dosing period is referred to as 1 cycle.

Study treatment will be administered only to eligible randomized patients at qualified centers (e.g., listed on the FDA Form 1572).

14.1.1 Starting Dose Assignment

The starting dose of ponatinib will be 45 mg (Cohort A), 30 mg (Cohort B), or 15 mg (Cohort C), taken orally once daily. Patients starting at 45 mg or 30 mg will have their daily dose reduced to 15 mg if ≤ 1% BCR-ABL1^{IS} has been achieved, as described in Section 14.1.3.

14.1.2 Treatment Administration

Patients will take the prescribed number of tablets with water, with or without food, at approximately the same time each day. Patients 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 should be instructed not to take their dose on days of visits where they will have plasma samples drawn for PK analyses until after the first sample is drawn. Patients who forget to take their dose more than 6 hours after it is due should not make up the missed dose. Any missed doses should be recorded, and subsequent training of patients should be documented in the appropriate source record (e.g., clinic chart) and in the eCRF.

14.1.3 Mandatory Dose Reduction for Response Scheme

Patients will be assessed for ≤ 1% BCR-ABL1^{IS} (as defined below) at 3-month intervals, and those in the 45 mg QD and 30 mg QD cohorts will have their doses reduced to 15 mg QD upon

attainment of ≤ 1% BCR-ABL1^{IS} during the Main Treatment Period (refer to Section 14.1.5 for dosing during the Treatment Continuation Period). Dose reduction based upon response can also be implemented when an unscheduled response assessment is performed. Dose reduction should be implemented as soon as feasible (preferably in 2-3 weeks from the time the response results have been communicated to the sites). An unscheduled visit may be required to implement this change. No dose reduction for response will be implemented for patients in the 15 mg QD cohort.

The primary endpoint of this study will be achievement of ≤ 1% BCR-ABL1^{IS} at 12 months. This incorporates standard CML approaches to patient care and uses patient monitoring. Increasingly, patient monitoring is being performed by quantitation of BCR-ABL1 transcripts from a standard established by the international scale (IS) (Marin, 2014; NCCN, 2014; Baccarani et al, 2013; Marin et al, 2012; Lauseker et al, 2012; Saglio et al, 2012).

Patients will undergo a baseline BM aspirate and cytogenetic assessment to establish their diagnosis and eligibility. They will then undergo molecular monitoring at 3-month intervals for the assessment of response and to inform the decision regarding dose reduction. Patients will undergo a BM aspirate with cytogenetic assessment after 12 cycles, and at additional time points as specified in the Schedule of Events (Table 8). Details of BM acquisition are also listed in Section 12.1, Item 16.

Note: Patients who begin therapy at 45 mg or 30 mg may undergo dose reduction *for adverse events* (see Section 14.2.2) prior to the achievement of ≤ 1% BCR-ABL1^{IS}. This should not affect the assessment of response (≤ 1% BCR-ABL1^{IS}) nor the mandated reduction to 15 mg QD upon its attainment.

The schedule of patient assessment for mandatory response-related dose reduction is as follows:

Patients in the 45 mg and 30 mg cohorts will have their dose reduced to 15 mg at 3 months if they have achieved ≤ 1% BCR-ABL1^{IS}. If not, they will continue at their current dose until the 6-month assessment.

At 6 months, they will have their dose reduced to 15 mg if they have achieved ≤ 1% BCR-ABL1^{IS}. If not, they will continue at their current dose until the 9-month assessment.

At 9 months, they will have their dose reduced to 15 mg if they have achieved ≤ 1% BCR-ABL1^{IS}. If not, they will continue at their current dose until the 12-month assessment.

At 12 months, patients will have their dose reduced to 15 mg if they have achieved ≤ 1% BCR-ABL1^{IS}.

Patients will discontinue therapy in the Main Treatment Period if they are not in ≤ 1% BCR-ABL1^{IS} at the time of molecular assessment at 12 months.

14.1.4 Loss of Response after Dose Reduction for ≤ 1% BCR-ABL1^{IS}

Patients who achieve ≤ 1% BCR-ABL1^{IS} at any time point, undergo dose reduction, and then lose ≤ 1% BCR-ABL1^{IS} (Section 16.5.1.1), are candidates for dose re-escalation to their starting

dose in the absence of AEs requiring dose modification and upon review and agreement with the medical monitor.

As described in Section 14.1.3, patients in the cohorts starting at 45 mg (Cohort A) and 30 mg (Cohort B) will undergo dose reduction to 15 mg upon achievement of ≤ 1% BCR-ABL1^{IS} during the Main Treatment Period. With continued monitoring at the reduced dose, should patients from Cohort A or Cohort B demonstrate loss of ≤ 1% BCR-ABL1^{IS} as determined by molecular assessment, they may be candidates for dose escalation. Dose escalation can be implemented at the discretion of the physician and upon review with the medical monitor.

Patients will be monitored with molecular response assessments according to the Schedule of Events (Table 7 and Table 8). If the assessment does not demonstrate loss of ≤ 1% BCR-ABL1^{IS}, as defined in Section 16.5.1.1, continued monitoring is indicated. If the assessment indicates loss of ≤ 1% BCR-ABL1^{IS}, dose escalation may be considered.

Patients may be dose re-escalated as follows:

Patients may only undergo dose re-escalation if they are in Cohort A or Cohort B and do not have ongoing AEs necessitating treatment at 10 mg or 15 mg as per Section 14.2.2 (Dose Modifications for Adverse Drug Reactions).

For patients in Cohort A, escalate to the starting dose of 45 mg. If patients underwent dose reduction for AEs and have not yet resumed dosing at 45 mg, escalate to 30 mg.

For patients in Cohort B, escalate to the starting dose of 30 mg.

For patients in Cohort C, loss of ≤ 1% BCR-ABL1^{IS} mandates their discontinuation from the Main Treatment Period.

If patients regain ≤ 1% BCR-ABL1^{IS} after dose escalation, continue their therapy at the escalated dose and monitor according to the Schedule of Events (Table 7 and Table 8).

If patients do not regain ≤ 1% BCR-ABL1^{IS} after 6 months of therapy at the escalated dose, they must be discontinued from the Main Treatment Period.

14.1.5 Treatment during the Treatment Continuation Period

During the Treatment Continuation Period, each patient should be administered the dose and most frequent schedule that is both tolerable and continues to provide evidence of clinical benefit to the patient, not to exceed the highest dose and frequency (QD) determined from the patient's experience in the Main Treatment Period. A reduced dose and/or dosing frequency may be administered during the Treatment Continuation Period upon discussion and agreement between the investigator and the medical monitor.

14.2 Supportive Care

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 an analysis of odds ratios (OR), the leading risk factors for serious AOEs are cardiovascular disorders, such as any history of myocardial infarction (MI) (OR=6.86), coronary artery disease (OR=7.14), or coronary

revascularization (OR=6.19). The ORs for serious AOEs are 3.53 for history of ischemic cerebrovascular disease, 3.78 for diabetes mellitus, 2.49 for hypertension, and 2.07 for hypercholesterolemia. Based on this analysis, the following supportive care recommendations are provided to decrease the risk of AOEs and VTEs for patients taking ponatinib.

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 being treated with ponatinib who have elevated glucose levels. The American Diabetes Association guidelines should be followed, and antidiabetic 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 2003).

Hypertension Treatment

Hypertension (HTN) may contribute to risk of arterial occlusive events. Patients who have HTN should be managed appropriately before initiating treatment. During ponatinib treatment, blood pressure elevations should be monitored and 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). Ponatinib treatment should be temporarily interrupted if HTN is not medically controlled (refer to Section 14.2.1.5 below for additional management recommendations). Patients may require urgent clinical intervention for HTN associated with confusion, headache, chest pain, or shortness of breath.

14.2.1 Management of Selected AEs

Dose reduction guidelines are outlined in Section 14.2.2. This section provides additional guidance for management of selected AEs for ponatinib.

Comprehensive assessments of any study drug-related AEs (adverse drug reactions) experienced by the patient will be performed throughout the course of the study. Anticipated adverse drug reactions that may be experienced are described in the current Investigator's brochure for Ponatinib. 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 symptoms should be reported on the AE page.

14.2.1.1 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, renovascular disorders

including renal artery stenosis, 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. Vascular occlusive adverse events were more frequent with increasing age and in patients with prior history of ischemia, hypertension, diabetes, or hyperlipidemia.

14.2.1.1.1 Arterial Occlusion and Thrombosis

Serious arterial occlusive AEs occurred in ponatinib-treated patients; some patients experienced events of more than 1 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 AEs were also reported in ponatinib-treated patients. Some patients developed stenosis of large arterial vessels of the brain (e.g., carotid, vertebral, or middle cerebral artery).

Serious peripheral arterial 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.

Monitor and aggressively treat factors that increase cardiovascular risks, 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 AE of MI, stroke, or urgent revascularization while on trial must be discontinued from the trial unless the investigator believes the potential benefits of ponatinib treatment are likely to exceed the risks of continued treatment for that individual patient and the patient has no other treatment options.

14.2.1.1.2 Venous Thromboembolism

Serious venous thromboembolic AEs occurred in ponatinib-treated patients, including deep venous thrombosis, pulmonary embolism, superficial thrombophlebitis, and retinal vein thrombosis. Consider dose modification or discontinuation of ponatinib in patients who develop serious venous thromboembolic AEs. Ponatinib should not be restarted in patients with serious venous occlusive AEs unless the investigator believes the potential benefit outweighs the risk of recurrent venous occlusions and the patient has no other treatment options.

14.2.1.2 Neuropathy

Serious peripheral and cranial neuropathic AEs have occurred in ponatinib-treated patients. In clinical trials, 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. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness. Consider interrupting ponatinib and evaluate if neuropathy is suspected.

14.2.1.3 Hepatotoxicity

Hepatotoxicity, most commonly manifested by reversible transaminase and alkaline phosphatase elevation and hyperbilirubinemia, has been observed with ponatinib. Monitoring of hepatic function is recommended, and laboratory abnormalities should be managed with dose interruption and/or dose reduction, according to Table 9.

14.2.1.4 CHF and Left Ventricular Dysfunction

Severe 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 ponatinib in patients who develop serious CHF.

14.2.1.5 Hypertension

Blood pressure should be monitored at each visit. HTN detected by at least 2 blood pressure measurements should be graded according to NCI CTCAE, v4.0, which defines HTN as a disorder characterized by a pathological increase in blood pressure: a repeated elevation in the blood pressure exceeding 150 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. HTN may also contribute to renovascular disorders, most commonly observed as renal artery stenosis. Renal artery stenosis has been observed in patients taking ponatinib; monitoring for significant or unexplained hypertension should therefore include an assessment for renal vascular disease. 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 9.

14.2.1.6 Ocular Toxicity

Serious ocular AE 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. Conduct comprehensive eye exams at baseline and when clinically indicated. See Table 9 for details.

14.2.1.7 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. Most cases of pancreatitis or elevated pancreatic enzymes occur within the first 2 months of treatment with ponatinib. 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 either improved to grade 1 or resolved. Patients with low-grade (NCI CTCAE, v4.0 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 9 for details.

14.2.1.8 Hemorrhage

Hemorrhagic events have occurred in patients receiving ponatinib. Most of these events occurred in patients with grade 4 thrombocytopenia. Interrupt administration in the case of serious or severe hemorrhage.

14.2.1.9 Fluid Retention and Edema

Ponatinib is 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 ponatinib as outlined in Table 9.

14.2.1.10 Cardiac Arrhythmias

Supraventricular tachyarrhythmias were reported in patients treated with ponatinib. 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 9).

14.2.1.11 Myelosuppression

Neutropenia, anemia, and thrombocytopenia have been observed in clinical studies of ponatinib in patients with CML. While myelosuppression can occur at 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 should occur (see Table 9). 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].

14.2.1.12 Tumor Lysis Syndrome (TLS)

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.

14.2.1.13 Rash and/or Pruritus

Skin rashes have been commonly reported to be associated with ponatinib. 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, 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 of ponatinib—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 9.

14.2.1.14 Diarrhea, Nausea, and Vomiting

Diarrhea is a common side effect of ponatinib, 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, then 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 ponatinib. The use of an antiemetic prophylactically is not recommended. However, if a patient is symptomatic, appropriate antiemetic medications may be used as clinically indicated.

14.2.1.15 Constitutional Symptoms/Joint Pain

Certain constitutional symptoms—such as myalgia, arthralgia, headache, weakness, fatigue, asthenia, and low-grade fever—have been very commonly reported with ponatinib. These symptoms have been reported mainly at the initiation of treatment, are typically short-lived (< 2 weeks), and are 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 their current dose of ponatinib, uninterrupted, and their symptoms can be managed with a short course of oral analgesics, corticosteroids, and/or antipyretics as clinically indicated. If dose interruption is indicated, patients can resume the same dose of ponatinib—typically without recurrence of symptoms—once the original episode has either improved or resolved.

14.2.1.16 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.

14.2.1.17 Posterior Reversible Encephalopathy Syndrome (PRES)

PRES, also known as reversible posterior leukoencephalopathy syndrome, is a neurological disorder that can present with signs and symptoms such as seizure, headache, decreased alertness, altered mental functioning, vision loss, and other visual and neurological disturbances. No cases of PRES have been reported in clinical trials conducted by ARIAD, but two postmarketing cases related to PRES have been reported in ponatinib-treated patients. If PRES is diagnosed, interrupt ponatinib treatment and resume treatment only once the event is resolved, and if the benefit of continued treatment outweighs the risk of PRES.

14.2.2 Dose Modifications for Adverse Drug Reactions

14.2.2.1 Dose Reduction Guidelines

Dose reduction guidelines for ponatinib are summarized in Table 9, and 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. Variation from these guidelines must be communicated with the sponsor or sponsor designee, ideally prior to implementation, but no later than 72 hours, and must be documented. 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 14.2.2.3.

Dose reduction below 10 mg once-daily is not permitted in the Main Treatment Period (see Table 9; a reduced dosing frequency may be permitted in the Treatment Continuation Period in accordance with Section 14.1.5). 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 7 and Table 8).

Once adverse drug reactions have resolved when the guidelines below are followed, investigators are encouraged to re-escalate the dose of ponatinib (Section 14.2.2.3).

Table 9 Dose Modifications for Adverse Drug Reactions

Toxicity	Modification
Nonhematologic Toxicity	
General	
Grade 1 or transient grade 2	No intervention
Grade 2 lasting ≥ 7 days with optimal care	First occurrence at any dose level: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level Recurrence* at 45 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 30 mg Recurrence at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Recurrence at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Recurrence at 10 mg: Discontinue ponatinib
Grade 3 or 4	Occurrence** at 45 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 30 mg Occurrence at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Occurrence at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Occurrence 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

Toxicity	Modification
Asymptomatic grade 3 or 4 elevation of lipase (> 2 × ULN) or asymptomatic radiologic pancreatitis (grade 2 pancreatitis)	Occurrence at 45 mg: Hold until event is ≤ grade 1 (≤ 1.5 x ULN), or has returned to baseline Resume at 30 mg Occurrence at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Occurrence at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Occurrence at 10 mg: Discontinue ponatinib
Symptomatic grade 3 pancreatitis (severe pain, vomiting, medical intervention indicated [e.g., analgesia, nutritional support])	Occurrence at 45 mg: Hold until complete resolution of symptoms and after recovery of lipase elevation to ≤ grade 1 Resume at 30 mg Occurrence at 30 mg: Hold until complete resolution of symptoms and after recovery of lipase elevation to ≤ grade 1 Resume at 15 mg Occurrence at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Occurrence at 10 mg: Discontinue ponatinib
Grade 4 pancreatitis	Discontinue ponatinib
Hepatic Toxicity	
Elevation of liver transaminase > 3 × ULN (grade 2 or higher)	Occurrence at 45 mg: Hold ponatinib and monitor hepatic function until event is ≤ grade 1 (≤ 3 ×ULN) Resume at 30 mg Occurrence at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Occurrence at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Occurrence 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

Toxicity	Modification
LVEF/CHF[1]	
Grade 1	No dose adjustment
Grade 2	First occurrence at any dose level: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level Recurrence* at 45 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 30 mg Recurrence at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Recurrence at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Recurrence at 10 mg: Discontinue ponatinib
Grade 3	Occurrence** at 45 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 30 mg Occurrence at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Occurrence at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Occurrence at 10 mg: Discontinue ponatinib
Grade 4	Discontinue ponatinib.
Skin rash	
Grade 1	No intervention

Toxicity	Modification
Grade 2 persistent despite optimal symptomatic therapy	First occurrence at any dose level: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level Recurrence at 45 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 30 mg Recurrence at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Recurrence at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Recurrence at 10 mg: Discontinue ponatinib
Grade 3 persistent despite optimal symptomatic therapy	First occurrence at any dose level: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level Recurrence at 45 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 30 mg Recurrence at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Recurrence at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Recurrence at 10 mg: Discontinue ponatinib
Hematologic Toxicity	
***Drug-Related* ANC/platelets**	
Grade 1 or 2	No dose adjustment

Toxicity	Modification
Grade 3 or 4	First occurrence at any dose level: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level Recurrence at 45 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 30 mg Recurrence at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Recurrence at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Recurrence at 10 mg: Discontinue ponatinib
* "Recurrence" means the second time an AE is encountered by a patient at a given dose level. ** "Occurrence" means the first time an AE is encountered by a patient at a given dose level. Definitions: ANC=absolute neutrophil count; CHF=congestive heart failure; CT=computed tomography; LVEF=left ventricular ejection fraction. [1]Note: NCI CTCAE, v4.0 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%.	

14.2.2.2 Dose Modifications for AOEs and VTEs

If a serious vascular occlusive adverse reaction occurs, treatment should be interrupted. Ponatinib should not be re-administered to patients with arterial or venous occlusive events unless the potential benefit outweighs the risk of recurrent arterial or venous occlusions.

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.

14.2.2.2.1 Arterial Occlusive Events

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

For all other arterial occlusive events, dose modification guidelines are outlined in Table 10.

Table 10 Dose Modifications for Arterial Occlusive Events

Arterial Occlusion: Other Cardiovascular and Cerebrovascular Events	
Grade 1	Consider interruption or dose reduction of ponatinib until the event resolves.
Grade 2	First occurrence** at any dose level: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level. Recurrence* at 45 mg: Discontinue study drug Recurrence at 30 mg: Discontinue study drug Recurrence at 15 mg: Discontinue study drug Recurrence at 10 mg: Discontinue study drug
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.
Grade 2	First occurrence at any dose level: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level Recurrence at 45 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 30 mg Recurrence at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Recurrence at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Recurrence at 10 mg: Discontinue ponatinib

Grade 3	Occurrence at 45 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 30 mg Occurrence at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Occurrence at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Occurrence at 10 mg: Discontinue ponatinib Any recurrence at any dose level, discontinue ponatinib
Grade 4	Discontinue ponatinib

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

14.2.2.2.2 Venous Thromboembolic Events

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, dose modification guidelines are outlined in Table 11.

Table 11 Dose Modifications for Venous Thromboembolic Events

Venous Thromboembolic Events	
Grade 1	Consider interruption or dose reduction of ponatinib until the event resolves.
Grade 2	First occurrence at any dose level: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level Recurrence* at 45 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 30 mg Recurrence at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Recurrence at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Recurrence at 10 mg: Discontinue ponatinib
Grade 3	Occurrence** at 45 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 30 mg Occurrence at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Occurrence at 15 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 10 mg Occurrence at 10 mg: Discontinue ponatinib
Grade 4	Discontinue ponatinib.

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

14.2.2.3 Dose Re-Escalation after Resolution of Adverse Drug Reactions

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

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

Patients may receive step-wise dose escalations (e.g., 10 mg QD to 15 mg QD to 30 mg QD) 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 arterial occlusion are not eligible for dose re-escalation after resolution of their symptoms.

14.3 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 the last dose of study drug or the investigator/patient decision to discontinue, whichever occurs later) are to be reported on the appropriate eCRF for each patient.

14.4 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)

14.5 Prohibited Treatment(s)/Therapy

The following concurrent medications and treatments are prohibited:

- Other anticancer therapies
- Other investigational drugs or devices
- Medications with a known risk of Torsades de Pointes (see Appendix A)
- Herbal preparations or related over-the-counter preparations containing herbal ingredients
- Elective surgery requiring inpatient care that cannot be postponed until study completion

Medications that are potent inhibitors or inducers of CYP3A4 (see Appendix B) should be avoided, but are not prohibited (see Section 14.6).

Medications that prolong the QT interval (see Appendix A), but are not associated with a known risk of Torsades de Pointes, should be avoided, but are not prohibited. If such medications are necessary and used while a patient is on study, additional ECG monitoring should be performed as clinically indicated.

14.6 Potential Drug Interactions

Based on in vitro studies, drug-drug interactions due to either CYP inhibition or induction by ponatinib are highly unlikely in clinical trials using the recommended daily doses of 15-45 mg. In vitro studies demonstrate that human CYP3A4 is involved in the metabolism of ponatinib. In light of this, a drug-drug interaction study was performed with a strong CYP3A4 inhibitor in healthy subjects, and ketoconazole co-administration was found to increase ponatinib C_{max} and AUC by 47% and 78%, respectively. Another drug-drug interaction study was performed with a strong CYP3A4 inducer in healthy subjects, and co-administration of ponatinib following multiple doses of rifampin was found to decrease ponatinib C_{max} and AUC by 42% and 62%, respectively. Since CYP3A4 contributes to the metabolism of ponatinib, strong inducers or inhibitors of CYP3A4 should be used with caution or avoided altogether. If co-administration with strong inhibitors of CYP3A4 is unavoidable, consider reduction of the ponatinib dose 1 level from the current dose (that is, 30 mg for a patient receiving 45 mg; 15 mg for a patient receiving 30 mg). Consider an alternative to the strong CYP3A4 inhibitor or, if that is not possible, consult the sponsor. Co-administration of strong CYP3A inducers with ponatinib should be avoided unless the benefit outweighs the risk of decreased ponatinib exposure. Patients should be monitored for reduced efficacy if co-administration with strong CYP3A inducers cannot be avoided. Selection of concomitant medication with no or minimal CYP3A induction potential is recommended.

Medications that are associated with the prolongation of the QT interval may interact with ponatinib, as well. Some medications associated with QT prolongation also interact with CYP3A4.

14.7 Treatment Supply

14.7.1 Formulation, Packaging, and Labeling

Ponatinib investigational drug product is supplied as tablets. Each tablet contains 10 mg, 15 mg, 30 mg, or 45 mg of ponatinib active ingredient. Other ingredients are typical pharmaceutical excipients (lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, 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 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

45 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.

14.7.2 Treatment Storage, Dispensing, and Accountability

Store ponatinib tablets at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Keep away from children.

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, tablet strength, the number of tablets 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.

In the event that a patient cannot visit the site to obtain the study drug due to unavoidable circumstances, such as the COVID-19 pandemic, sites should contact the study monitor/designee to arrange for an alternate mechanism (eg, DTP Shipping).

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

No other utilization of ponatinib 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.

14.7.2.2 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 trial, a final study drug accountability review will be conducted. Any discrepancies must be investigated and all unused

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

15 ADVERSE EVENT REPORTING

15.1 AEs

15.1.1 AE 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 pre-existing condition that is temporally associated with the use of the study drug (e.g., occurs after the first dose of study drug), is also defined as an AE.

AEs 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 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 AE 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 a 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 adverse events of special interest [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 SAEs 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 AE Severity

The severity of AEs will be assessed according to the NCI CTCAE, v4.0 (see Appendix C and the Study Reference Manual). If the AE is not defined in the CTCAE, the investigator will determine its severity 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 Expectedness

The expectedness of an SAE is assessed by the sponsor in the overall classification of SAEs for regulatory reportability. The current Clinical Investigator's Brochure will be used as the reference for determination of expectedness and risk assessment for ponatinib.

15.2 Serious Adverse Events (SAEs) and Adverse Events of Special Interests (AESIs)

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 Events Definition

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

An AE is considered an SAE if at least one of these 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 (i.e., this does not include an event that, had it occurred in a more severe form, might have caused death)

- *Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions*: Any substantial disruption of a 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 in the trial (i.e., does not include metastatic or progressive disease)
- *Important medical event:* Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not result in death, be life-threatening, or require hospitalization. However, if it is determined that the event may jeopardize the patient and/or may require intervention to prevent one of the other outcomes listed in the definition above, 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.

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

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

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

15.2.2 AESIs

AOEs and VTEs have been identified as AESIs for ponatinib. These include arterial and venous thrombotic and occlusive adverse events that meet the criteria for SAEs, as defined above in Section 15.2.1, as well as those AEs that do not meet the SAE criteria.

AESIs require ongoing monitoring by investigators and rapid identification and communication by the investigator to the sponsor. The sponsor has determined that the events listed below should be considered AESIs:

- Myocardial infarction (MI): The Third Universal Definition of Myocardial Infarction (Thygesen et al, 2012) is used to define MI. The term "Acute MI" is used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia including any one of the following:
  - A rise and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least 1 value above the 99th percentile upper reference limit (URL) and with at least one of the following:
    - Symptoms of ischemia
    - New or presumed new significant ST-segment T-wave changes or new left bundle branch block (LBBB)
    - Development of pathological Q waves in the ECG
    - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
    - Identification of an intracoronary thrombus by angiography or autopsy.
  - Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained or would be increased.
  - Percutaneous coronary intervention-related MI was arbitrarily defined by elevation of cTn values (>5 × 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values were elevated and were stable or falling. In addition, either (1) symptoms suggestive of myocardial ischemia, (2) new ischemic ECG changes, (3) angiographic findings

consistent with a procedural complication, or (4) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality were required.

- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least 1 value above the 99th percentile URL.
- Coronary artery bypass grafting-related MI was arbitrarily defined by elevation of cardiac biomarker values (>10 × 99th percentile URL) in patients with normal baseline cTn values (<99th percentile URL). In addition, either (1) new pathological Q waves or new LBBB, (2) angiographic documented new graft or new native coronary artery occlusion, or (3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

- 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 (e.g., 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 (e.g., pulmonary embolism, portal vein thrombosis, or renal vein thrombosis), or symptoms that may reflect venous thrombosis.

Additionally, the sponsor has a list of a broad range of nonspecific terms that could meet the criteria for AOEs and VTEs. The sponsor will periodically look at the safety data and inform the site if any AE qualifies for AOEs/VTEs as per that criteria. Dose modification guidelines for AOEs/VTEs are presented in Section 14.2.2.2.

15.2.3 Reporting SAEs

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

15.2.4 Information to be Provided by the Investigator for an SAE

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

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

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

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

15.2.5 Follow-up Information on a SAE

Appropriate diagnostic tests should be performed and therapeutic measures, as medically indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out until the event has resolved or is otherwise explained by the investigator. For all SAEs, the investigator is obligated to pursue and provide information to 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, provided 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

Routine follow-up should be conducted through and including 30 days after the last administration of assigned study treatment in the trial or the investigator/patient decision to discontinue treatment—whichever occurs later—in all patients, in order to monitor for the occurrence of SAEs. If an SAE continues after the 30-day evaluation period, 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.

Expedited Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

ARIAD, as study sponsor, is responsible for reporting suspected, unexpected, 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.

15.3 Other Safety Issues

15.3.1 Contraception and Pregnancy

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 as 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 the 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 should be advised to take a pregnancy test if their period is late, and to inform their investigator of the result.

If a patient is confirmed pregnant during the trial, 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 a Pregnancy Form. Initial information regarding a pregnancy must be immediately forwarded to ARIAD Drug Safety and Pharmacovigilance 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 trial. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

15.3.2 Overdose

An overdose is defined as the accidental or intentional ingestion or infusing of any dose of study treatment that exceeds the dose described in the protocol. Overdoses are not considered AEs; however, all overdoses should be recorded on an Overdose Form and forwarded to ARIAD Pharmacovigilance and Risk Management or its designated representative within 24 hours. An overdose should be reported even if it does not result in an AE. Overdoses do not need to be recorded on the eCRF; dosing information is recorded on the form.

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.

Eligible CP-CML patients will be randomized to 3 dose cohorts (45 mg, 30 mg, and 15 mg). Patients starting at 45 mg or 30 mg will have their daily dose reduced to 15 mg upon achievement of ≤ 1% BCR-ABL1^{IS}. Each cohort of patients will be analyzed separately for efficacy and safety.

Categorical data will be summarized by the number and percentage of patients in each category. Continuous variables will be summarized by descriptive statistics, including mean, standard deviation, median, and range.

Statistical inference will be made for each of the 3 cohorts separately—each with the primary endpoint of ≤ 1% BCR-ABL1^{IS} tested at 2-sided 0.05/3=0.0167 significance level, using the

Bonferroni method for multiplicity adjustment. The primary analysis of the primary endpoint of ≤ 1% BCR-ABL1^{IS} will be performed using a 2-sided exact 98.3% CI for ≤ 1% BCR-ABL1^{IS} rate based on the ITT population followed through the Main Treatment Period. Any other comparisons will be descriptive. An interim analysis (IA) is planned for this study after all patients have been enrolled in the study. The IA data summary will be descriptive in nature. The primary analysis is planned to be performed when all patients have at least 12 months of treatment. Additional analyses may be performed at later time points to develop additional CSRs as per sponsor's discretion. In addition, the data will be summarized and reported at least annually.

16.2 Analysis Populations

ITT Population: The ITT population will include all randomized patients, regardless of whether they take the assigned study drug. The primary analyses of efficacy will be based on this population. Randomized patients without response assessments will be considered as non-responders in the primary efficacy analysis (see Section 16.5.2.1).

Treated Population: The treated population for each cohort includes all patients who have received at least one dose of study drug. The primary analyses of safety will be based on this 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 anticancer therapy concurrent with study drug, or administration of incorrect dose [e.g., 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

- ≤ 1% BCR-ABL1^{IS} at 12 months

Secondary Endpoints

- MMR at 12 and 24 months, MCyR by 12 months and duration of MMR
- Safety evaluated by rates of AOEs and VTEs, AEs, and SAEs

Other Secondary Endpoints

- CCyR at 12 months
- Molecular responses: MMR, MR4, and MR4.5 by and at 3-month intervals and MR1 at 3 months
- CHR at 3 months
- Tolerability evaluated by discontinuation rate due to AEs, dose reductions due to AE, and dose interruptions

- Duration of Response:
  - Rates of ≤ 1% BCR-ABL1^{IS} by 12 months and at and by 6, 18, and 24 months
  - MMR at and by 6 and 18 months; and by 12 and 24 months
- Time to response and duration of response in responders, rate of progression to AP- or BP-CML, PFS, and OS

Exploratory Endpoints

CCI

[redacted]

16.4 Determination of Sample Size

The primary endpoint for this trial is ≤ 1% BCR-ABL1^{IS} at 12 months. Consistent with the phase 2 PACE trial, the null or uninteresting ≤ 1% BCR-ABL1^{IS} rate is set at 20%. The alternative ≤ 1% BCR-ABL1^{IS} rate is set at 35%. Using the Bonferroni method, the overall 2-sided significance level for statistical testing in each cohort will be set at 0.0167. The primary analysis of the primary endpoint of ≤ 1% BCR-ABL1^{IS} will be performed using a 2-sided exact 98.3% CI for ≤ 1% BCR-ABL1^{IS} rate based on the ITT population.

A total sample size of 276 patients or 92 patients in each cohort (1:1:1) will distinguish a favorable ≤ 1% BCR-ABL1^{IS} rate of 35% from a null or an uninteresting ≤ 1% BCR-ABL1^{IS} rate of 20% with a nominal 80% power and a 1-sided type I error rate of 0.0083 (equivalent to a 2-sided 0.0167) using an exact binomial test. Using the 20% boundary for ≤ 1% BCR-ABL1^{IS}, 29 or more ≤ 1% BCR-ABL1^{IS} responders will be needed for a lower limit of the 2-sided exact 98.3% CI for the ≤ 1% BCR-ABL1^{IS} rate to exceed 20%.

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 and windows for the time point assessments, will be provided in the statistical analysis plan (SAP).

16.5.1.1 Molecular Response Definitions

Rate of ≤ 1% BCR-ABL1^{IS} at 12 months is the proportion of patients achieving ≤ 1% BCR-ABL1^{IS} at 12 months after initiation of study drug.

Molecular Response: ≤ 1% BCR-ABL1^{IS}, MMR, MR4, and MR4.5 are defined as ≤1%, ≤ 0.1%, ≤ 0.01%, and ≤ 0.0032% BCR-ABL^{IS}, respectively. In the case of undetectable BCR-ABL transcript levels, a minimum of 10,000 and 32,000 ABL copies must be present in

order to be classified as MR4 and MR4.5, respectively. **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.

Time to ≤ 1% BCR-ABL1^{IS} is defined as the interval between the first dose date of the study treatment and the first date at which the criteria for ≤ 1% BCR-ABL1^{IS} are met.

Time to MMR is defined as the interval between the first dose date of the study treatment and the first date at which the criteria for MMR are met.

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

Loss of ≤ 1% BCR-ABL1^{IS} is 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 with progression to accelerated or blast phase 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 with progression to accelerated or blast phase 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 with progression to accelerated or blast phase or death due to CML.

16.5.1.2 Cytogenetic Response Definitions

MCyR by 12 months is the proportion of patients achieving CCyR or PCyR at any time within 12 months after initiation of study drug. Patients entering the study already in a PCyR must achieve a CCyR in order to be considered a success for achieving a MCyR.

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

- CCyR: 0% Ph+ metaphases
- PCyR: > 0 to 35% Ph+ metaphases

CCyR at 12 months is the proportion of patients achieving CCyR at 12 months after initiation of study drug.

16.5.1.3 Hematologic Response Definitions

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 < 450,000/mm^3
- 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 > 20,000/mm^3
- Platelet count that rises to ≥ 600,000/mm^3
- Splenomegaly progressing 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

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 the accelerated phase or blast phase of CML), or death due to any cause, censored at the last response assessment.

Progression to AP 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 × 10^9 platelets/L in peripheral blood unrelated to therapy

  or

- Cytogenetic, genetic evidence of clonal evolution

and

- No extramedullary disease

Progression to BP is defined as:

- ≥ 30% blasts in peripheral blood or bone marrow

or

- Extramedullary disease other than hepatosplenomegaly

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 when the patient was alive.

16.5.2 Primary Endpoint Analysis

The primary endpoint for each cohort is ≤ 1% BCR-ABL1^{IS} rate at 12 months. The 2-sided type I error adjusted for the 3 statistical tests, using the Bonferroni method, will be set at 0.05/3=0.0167. Analysis of ≤ 1% BCR-ABL1^{IS} rate will be performed using a 2-sided 98.3% exact CI. The point estimate of ≤ 1% BCR-ABL1^{IS} rate and a 98.3% exact CI, based on the exact binomial distribution (Clopper-Pearson exact CI), will be presented. Ponatinib will be considered promising if the lower limit of 2-sided 98.3% exact CI for the ≤ 1% BCR-ABL1^{IS} rate exceeds 20%. A 2-sided exact 95% CI will also be provided.

The primary analysis population for the primary efficacy endpoint will be based on the ITT population. The analysis for the primary endpoint will also be performed using the per-protocol population.

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

The following rules will be implemented for the primary analysis of ≤ 1% BCR-ABL1^{IS} in CP-CML patients:

- Patients for whom BCR-ABL1^{IS} cannot be determined (i.e., patients with BCR-ABL1 variants other than b2a2 or b3a2) will be excluded from the primary analysis
- Patients who are ≤ 1% BCR-ABL1^{IS} at baseline will be excluded from the primary analysis
- Patients will be considered as non-responders if they meet any of the following criteria:
    - Are randomized but untreated
    - Do not respond at 12 months after the initiation of study treatment
    - Undergo no baseline PCR assessment

16.5.3 Secondary Efficacy Endpoint Analyses

16.5.3.1 Secondary Efficacy Endpoints

Analyses of secondary response endpoints, such as MCyR, CCyR, MMR, and CHR, will be performed in the same way as the primary endpoint. For the secondary endpoints of time to ≤ 1% BCR-ABL1^{IS} and time to MMR, descriptive statistics will be provided for patients who meet the criteria for response. For the secondary endpoints of duration of ≤ 1% BCR-ABL1^{IS}, and MMR, the Kaplan-Meier method will be used to estimate duration of response among patients meeting the criteria for response. Rates of patients remaining in MCyR, ≤ 1% BCR-ABL1^{IS} and MMR at 12, 18, and 24 months, respectively, as well as the proportion of patients meeting MCyR by 12 months and CCyR at 12 months by BM cytogenetics, will be presented. The rate of progression to AP or BP will be summarized. PFS and OS will also be estimated, using the Kaplan-Meier method. Median time to event and its 2-sided 95% CI will be provided. The analyses of time to event and duration of response will be conducted for each dose cohort, and for descriptive purposes only.

The analyses of secondary efficacy endpoints will be performed on the ITT population. The analyses of secondary endpoints may also be performed on the per-protocol population.

16.5.3.2 Data Handling Rules for Secondary Efficacy Endpoint Analyses

The following rules will be implemented for the primary analysis of the secondary endpoints of MCyR and CCyR in CP-CML patients:

- Patients will be excluded from the analysis if they meet any of the following criteria:
    - Have fewer than 20 metaphases examined at baseline
    - Are in CCyR at baseline
    - Undergo no baseline cytogenetic assessment
    - Have a variant translocation that is not assessable for cytogenetic response
- Patients will be considered as non-responders if they meet any of the following criteria:
    - Are randomized but untreated
    - Do not respond by 12 months after the initiation of study treatment
- At any given cytogenetic assessment after baseline, if fewer than 20 metaphases are examined, the following rule will apply to the determination of MCyR:

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

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

For the primary analyses of secondary endpoints of MMR, MR4.5, MR4, and CHR, if patients do not have a post-baseline response assessment, they will be considered 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 SAP). Subgroups may include:

- Age (< 60 years, ≥ 60 years)
- Gender
- Race
- Geographic region
- T315I (Yes, No)
- Number of prior approved TKI therapies (1, 2, 3, 4)
- Other disease-related prognostic factors

16.5.5 Exploratory Analysis on Treatment Continuation Period

For efficacy in patients entering the optional Treatment Continuation Period, analyses will be performed by descriptive summary. PFS and OS will also be estimated based on data collected up to 5 years after the last patient enters the study, using the Kaplan-Meier method. The analyses of time to event and duration of response will be conducted for descriptive purposes only.

16.6 Safety Analysis

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. 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 TEAEs, and all AEs will be listed.

16.6.1 Analysis of AOEs and VTEs

Number and percentages of patients who developed AOEs and VTEs will be summarized for each cohort. These events will be categorized as follows:

- Arterial occlusive events
  - Cardiac occlusive/thrombotic events
  - Cerebral occlusive/thrombotic events
  - Peripheral occlusive/thrombotic events

- Venous thrombotic events

Details for classification of specific events as AOEs and VTEs are provided in Section 14.2.1.1.

Crude and exposure-adjusted incidence rates of AOEs and VTEs will be calculated for each cohort and for all patients. The exposure-adjusted incidence rate is calculated as number of patients with the AE divided by total treatment exposure time.

The following additional descriptive analyses will be performed to characterize AOEs and VTEs:

- **Time to onset**: Calculated as date of first AOE or VTE – first dose date + 1
- **Dose at onset**: Dose of ponatinib taken immediately prior to onset of first AOE or VTE

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

Baseline risk factors for the occurrence of AOEs and VTEs will be evaluated for all patients, and will include:

- History of ischemic disease
- History of non-ischemic cardiac disease
- Hypertension
- History of diabetes
- History of smoking
- Obesity
- History of hypercholesterolaemia
- Age
- Gender
- Other risk factors

16.6.2 Analysis of Categories of AEs

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 each cohort. 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 TEAEs 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 shifts in laboratory parameters from baseline to worst post-baseline value (in terms of NCI CTCAE, v.4.0 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 Analyses of Treatment Discontinuation Rate due to AEs, Dose Reductions, and Dose Interruptions

For each dose cohort, 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 in order to characterize length of dose interruptions and reductions.

16.7 Exposure-Response Analysis

The plasma concentration-time data will be listed and summarized by time point. These data will contribute to population PK and exposure-response analyses of safety (e.g., AOE incidence) and efficacy (e.g., MMR). The analysis plan for the population PK and exposure-response analyses will be defined separately and the results of these analyses will be reported separately.

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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 (CSR).

Protocol deviations related to the COVID-19 pandemic will be assessed and listed independently. Additional sensitivity analyses may be performed to evaluate the impact of protocol deviations related to COVID-19 on the primary efficacy and safety endpoints.

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 or its designee, as well as the investigator, will review the protocol; the Clinical Investigator's Brochure; the eCRFs and instructions for their completion; the procedure for obtaining informed consent; and the procedure for reporting AEs. A qualified representative of the sponsor will monitor the conduct of the study by both visiting the site and contacting it 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 (e.g., sponsor, IRB/EC, or other investigators) who accepts the responsibility. The sponsor must be notified in writing of and agree to the change in advance. An updated FDA Form 1572 will be filed with the sponsor and the FDA for any changes in the study personnel reported in the current FDA Form 1572.

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)

In the event that a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic, alternative monitoring approaches such as remote source data verification or telephone contact may be used to ensure data quality and integrity and maintain patient safety. Alternative monitoring approaches should be used as approved by the sponsor, and only where allowed by the local Health Authority, local privacy laws (where applicable), and the IRB/IEC.

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 (i.e., list the investigator's name, the protocol number and title, the date of the protocol and informed consent document, and the date of approval of the protocol and the informed consent document). Any advertisements used to recruit patients should also be reviewed by the IRB/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 provides to the investigator, as well as all information generated in connection with the study, must be kept confidential and must not be disclosed to a third party without the prior written consent of the sponsor. In addition, this

information must not be 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 (DMC)

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

The DMC will be responsible for evaluating the results of safety analyses and making 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.

18.4.2 Study Steering Committee

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

18.4.3 Cardiovascular Endpoint Adjudication Committee

The cardiovascular endpoint adjudication committee (CVEAC) will be composed of independent experts with experience and training appropriate for reviews of the CV, AOE, HF, and VTE endpoints. They will review all CV events defined as AOEs, HF, and VTEs reported by the sites (i.e., initial diagnoses, laboratory values, results of procedures, hospital discharge summaries) to determine the occurrence of CV endpoints and sites may be requested to send relevant source data to the sponsor representative for this purpose. The adjudication of these events will be performed based on the CVEAC adjudication charter, which will document details for performing adjudication. The CVEAC's assessment of each potential CV endpoint will be documented in the clinical database and will be used in the endpoint analysis. The process will

be coordinated by the contract research organization, and the CVEAC charter will define the endpoints and the responsibilities of the committee.

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

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

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

Section 801 of the FDA Amendments Act mandates the registration with ClinicalTrials.gov of certain clinical trials of drugs (including biological products) and medical devices subject to FDA regulations for any disease or condition. The International Committee of Medical Journal Editors (ICMJE) requires trial registration as a condition for publication of research results generated by a clinical trial (icmje.org [Accessed: 21 March 2014]).

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 Torsades de Pointes

Four categories of QT-prolonging drugs that may be used as a guide for this protocol can be accessed at crediblemeds.org/everyone/composite-list-all-qtdrugs/ [Accessed: 04 September 2020]. Categories include "Drugs with Known TdP Risk," "Drugs with Possible TdP Risk," "Drugs with Conditional TdP Risk," and "Drugs to be Avoided by Congenital Long QT Patients." The investigator site should register (under the "For Healthcare Providers" tab) to access these categories. If the investigator site does not wish to register, a composite list, including all categories, is available.

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

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

Table A-1 Drugs Generally Accepted by the QTDrugs.org Advisory Board of the Arizona CERT to have a Known Risk of Causing Torsades de Pointes; Prohibited in this Study

Generic Name	Brand Name	Class/Clinical Use
Aclarubicin	Aclacin®, Aclacinomycine®, Aclacinon®, Aclaplastin®, Jaclacin®	Anticancer/cancer
Amiodarone	Cordarone®, Pacerone®, Nexterone®	Antiarrhythmic/arrhythmia
Anagrelide	Agrylin®, Xagrid®	Phosphodiesterase 3 inhibitor/thrombocythemia
Arsenic trioxide	Trisenox®	Anticancer/leukemia
Astemizole	Hismanal®	Antihistamine/allergic rhinitis
Azithromycin	Zithromax®, Zmax®	Antibiotic/bacterial infection
Bepridil	Vascor®	Antianginal/angina pectoris (heart pain)
Cesium chloride	Energy Catalyst	Toxin/cancer
Chloroquine	Aralen®	Antimalarial/malaria
Chlorpromazine	Thorazine®, Largactil®, Megaphen®	Antipsychotic/Antiemetic/schizophrenia, nausea, others
Chlorprothixene	Truxal®	Antipsychotic/schizophrenia

Generic Name	Brand Name	Class/Clinical Use
Cilostazol	Pletal®	Phosphodiesterase 3 inhibitor/intermittent claudication
Ciprofloxicin	Cipro®, Cipro-XR®, Neofloxin	Antibiotic/bacterial infection
Cisapride	Propulsid®	GI stimulant/increase GI motility
Citalopram	Celexa®, Cipramil®	Antidepressant, SSRI/depression
Clarithromycin	Biaxin®, Prevpac®	Antibiotic/bacterial infection
Cocaine	Cocaine	Local anesthetic/topical anesthetic
Disopyramide	Norpace®	Antiarrhythmic/arrhythmia
Dofetilide	Tikosyn®	Antiarrhythmic/ arrhythmia
Domperidone	Motilium®, Motillium®, Motinorm Costi®, Nomit®	Antiemetic/nausea, vomiting
Donepezil	Aricept®	Cholinesterase inhibitor/Dementia (Alzheimer's disease)
Dronedarone	Multaq®	Antiarrhythmic/ arrhythmia
Droperidol	Inapsine®, Droleptan®, Dridol®, Xomolix®	Antipsychotic/Antiemetic/anesthesia (adjunct), nausea
Erythromycin	E.E.S.®, Robimycin®, EMycin®, Erymax®, Ery-Tab®, Eryc Ranbaxy®, Erypar®, Eryped®, Erythrocin Stearate Filmtab®, Erythrocot®, E-Base®, Erythroped®, Ilosone®, MY-E®, Pediamycin®, Abboticin®, Abboticin-ES®, Erycin®, PCE Dispertab®, Stiemycine®, Acnasol®, Tiloryth®	Antibiotic /bacterial infection, increase GI motility

Generic Name	Brand Name	Class/Clinical Use
Escitalopram	Cipralex®, Lexapro®, Nexito®, Anxiset-E®, Exodus®, Esto®, Seroplex®, Elicea®, Lexamil®, Lexam®, Entact®, Losita®, Reposil®, Animaxen®, Esitalo®, Lexamil®	Antidepressant, SSRI/major depression, anxiety disorders
Flecainide	Tambocor®, Almarytm®, Apocard®, Ecrinal®, Flécaine®	Antiarrhythmic/arrhythmia
Fluconazole	Diflucan®, Trican®	Antifungal/fungal infection
Gatifloxacin	Tequin®	Antibiotic/bacterial infection
Grepafloxacin	Raxar®	Antibiotic/bacterial infection
Halofantrine	Halfan®	Antimalarial/malaria
Haloperidol	Haldol®, Aloperidin®, Bioperidolo®, Brotopon®, Dozic®, Duraperidol®, Einalon S®, Eukystol®, Halosten®, Keselan®, Linton®, Peluces®, Serenace®, Serenase®, Sigaperidol®	Antipsychotic/schizophrenia, agitation
Hydroquinidine (dihydroquinidine)	Serecor®	Antiarrhythmic/arrhythmia
Hydroxychloroquine	Plaquenil®, Quineprox®	Antimalarial, Antiinflammatory/malaria, SLE, rheumatoid arthritis
Ibogaine		Psychedelic/narcotic addiction, unproven
Ibutilide	Corvert®	Antiarrhythmic/arrhythmia
Levofloxacin	Levaquin®, Tavanic®	Antibiotic/bacterial infection
Levomepromazine (methotrimeprazine)	Nosinan®, Nozinan®, Levoprome®	Antipsychotic/schizophrenia

Generic Name	Brand Name	Class/Clinical Use
Levomethadyl acetate	Orlaam®	Opioid agonist/narcotic dependence
Levosulpiride	Lesuride®, Levazeo®, Enliva®	Antipsychotic/schizophrenia
Mesoridazine	Serentil®	Antipsychotic/schizophrenia
Methadone	Dolophine®, Symoron®, Amidone®, Methadose®, Physeptone®, Heptadon®	Opioid agonist/pain, narcotic dependence
Moxifloxacin	Avelox®, Avalox®, Avelon®	Antibiotic/bacterial infection
Nifekalant	Shinbit®	Antiarrhythmic/arrhythmia
Ondansetron	Zofran®, Anset®, Ondemet®, Zuplenz®, Emetron®, Ondavell®, Emeset®, Ondisolv®, Setronax®	Antiemetic/nausea, vomiting
Oxaliplatin	Eloxatin®	Anticancer/cancer
Papaverine HCl (intracoronary)		Vasodilator, Coronary/diagnostic adjunct
Pentamidine	Pentam®	Antifungal/fungal infection (pneumocystis pneumonia)
Pimozide	Orap®	Antipsychotic/Tourette's disorder
Probucol	Lorelco®	Antilipemic/hypercholesterolemia
Procainamide	Pronestyl®, Procan®	Antiarrhythmic/arrhythmia
Propofol	Diprivan®, Propoven®	Anesthetic, general/anesthesia
Quinidine	Quinaglute®, Duraquin®, Quinact®, Quinidex®, Cin-Quin®, Quinora®	Antiarrhythmic/arrhythmia

Generic Name	Brand Name	Class/Clinical Use
Roxithromycin	Rulide®, Xthrocin®, Roxl-150®, Roxo®, Surlid®, Rulide®, Biaxsig®, Roxar®, Roximycinv®, Roxomycin®, Rulid®, Tirabicin®, Coroxin®	Antibiotic/bacterial infection
Sevoflurane	Ulane®, Sojourn®	Anesthetic, general/anesthesia
Sotalol	Betapace®, Sotalex®, Sotacor®	Antiarrhythmic/arrhythmia
Sparfloxacin	Zagam®	Antibiotic/bacterial infection
Sulpiride	Dogmatil®, Dolmatil®, Eglonyl®, Espiride®, Modal®, Sulpor®	Antipsychotic, atypical/schizophrenia
Sultopride	Barnetil®, Barnotil®, Topral®	Antipsychotic, atypical/schizophrenia
Terfenadine	Seldane®	Antihistamine/Allergic rhinitis
Terlipressin	Teripress®, Glypressin®, Terlipin®, Remestyp®, Tresil®, Teriss®	Vasoconstrictor/septic shock
Terodiline	Micturin®, Mictrol®	Muscle relaxant/bladder spasm
Thioridazine	Mellaril®, Novoridazine®, Thioril®	Antipsychotic/schizophrenia
Vandetanib	Caprelsa®	Anticancer/thyroid cancer

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 medicine.iupui.edu/clinpharm/ddis/table.aspx [Accessed 21 March 2014]. 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, v4.0) can be found on the following website:

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).

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Approval	07-Oct-2020 17:54 UTC
	Biostatistics Approval	07-Oct-2020 19:19 UTC
	Clinical Pharmacology Approval	08-Oct-2020 01:31 UTC