Title: A phase I/II multi-center, open-label study of ponatinib in Japanese patients with chronic myeloid leukemia (CML) who have failed dasatinib or nilotinib or Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) who have failed prior tyrosine kinase inhibitors (TKIs)

NCT Number: NCT01667133

Protocol Approve Date: 21 November 2013

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

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

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

CLINICAL STUDY PROTOCOL

Study Title:	A phase I/II multi-center, open-label study of ponatinib in Japanese patients with chronic myeloid leukemia (CML) who have failed dasatinib or nilotinib or Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) who have failed prior tyrosine kinase inhibitors (TKIs)
Protocol Number:	AP24534-11-106
Study Phase:	I/II
Product Name:	AP24534
Sponsor:	ARIAD Pharmaceuticals, Inc 26 Landsdowne Street Cambridge, MA 02139-4234 Telephone: +1 (617) 494-0400
In-Country Clinical Caretaker (ICCC):	PPD
Protocol Issue Date:	21 November 2013
Version Number:	Version 3.0

PROTOCOL REVISION HISTORY

Amendment Number	Protocol Version Number	Date
First Version	Version 1.0	08 May 2012
Revision in line with PMDA Advice raised during the CTN inquiry	Version 1.1	31 May 2012
Revision for appropriate writing	Version 1.2	11 Jun 2012
Revision for appropriate writing	Version 1.3	04 Jul 2012
Amendment 1	Version 2.0	26 June 2013
Amendment 2	Version 3.0	21 November 2013

CONTACT INFORMATION

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In-Country Clinical Caretaker (ICCC):	PPD
Monitor:	PPD

PROTOCOL SYNOPSIS

Study Title	A phase I/II multi-center, open-label study of ponatinib in Japanese patients with chronic myeloid leukemia (CML) who have failed dasatinib or nilotinib or Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) who have failed prior tyrosine kinase inhibitors (TKIs)
Study Treatment	AP24534 (Ponatinib 15 mg or 45 mg white tablets; once daily)
Phase	Phase I/II
Eligible Population	Japanese patients with CML who have experienced a failure of dasatinib or nilotinib because of resistance or intolerance, or Ph+ ALL patients who have experienced a failure of prior TKIs because of resistance or intolerance
Summary and Study Rationale	Chronic myeloid leukemia is a clonal myeloproliferative disorder that represents about 15% of adult leukemias (Deininger et al, 2000). The underlying cause of CML is the Breakpoint Cluster Region-Abelson (BCR-ABL) fusion oncoprotein, which results from a reciprocal (9;22) chromosomal translocation in hematopoietic stem cells. This chromosomal abnormality (Ph+) is present in about 95% of all patients with CML, as well as about 40% of adult patients with Ph+ ALL. The translocation leads to the fusion of the BCR coding sequence with the tyrosine kinase coding region of ABL. This fusion event results in the constitutive activation of ABL kinase activity, which is both necessary and sufficient for induction of CML or ALL (Deininger et al, 2000). Imatinib was the first small molecule TKI approved by the Food and Drug Administration (FDA; United States) to treat CML patients. At 8 years of follow-up, the pivotal study of imatinib (IRIS: International Randomized Study of Interferon and ST1571 trial) in newly diagnosed chronic phase (CP)-CML patients has reported 81% event-free survival (EFS) and 85% overall survival (OS; Cortes et al, 2011). However, despite the success of imatinib, 45% of patients in the IRIS trial discontinued imatinib therapy. A substantial fraction of patients either initially fail to respond to imatinib or progress after a period of therapy. BCR-ABL point mutations in the ABL kinase domain that impair imatinib binding are the main cause of resistance to imatinib therapy, and account for approximately 40% to 50% of resistant cases of disease (Branford et al, 2003; Jabbour et al, 2006; Jones et al, 2009; Terasawa et al, 2010; O'Hare et al, 2011). Second-generation small-molecule inhibitors, dasatinib and nilotinib, are more potent than imatinib and inhibit many, but not all, imatinib-resistant point mutants, as well as native BCR-ABL (Talpaz et al, 2006; Kantarjian et al, 2006). Dasatinib and nilotinib were approved in Japan in 2009. Both are approved for use in patients who have experienced a failure of imatinib therapy, based on phase II clinical trials, in which approximately 40% to 45% of CP-CML patients achieved major cytogenetic responses (MCyRs) (Pinilla-Ibarz et al, 2008; Kantarjian et al, 2007). However, the remainder of patients, many of whom carry resistance mutations, remained refractory. Of note, both dasatinib and nilotinib are ineffective against the uniformly resistant T315I BCR-ABL mutation, which represents 15% to 20% of all clinically observed mutations (O'Hare et al, 2007). To address the problem of resistance to the first- and second-generation BCR-ABL TKIs, ARIAD Pharmaceuticals, Inc (ARIAD) has developed ponatinib. Ponatinib is a novel synthetic orally active TKI, specifically developed to inhibit BCR-ABL, the fusion protein that is the product of the Philadelphia chromosome in CML and in a subset of ALL. It potently inhibits the BCR-ABL protein, as well as mutated forms of the protein that arise in patients resistant to prior therapies with TKIs; for this reason, it

	is a pan-BCR-ABL inhibitor. In vitro assays have demonstrated that ponatinib potently inhibits the enzymatic activity of the T315I ABL kinase domain, as well as that of the native (unmutated) enzyme. In leukemia cell lines expressing these BCR-ABL variants, ponatinib potently inhibited BCR-ABL signaling, leading to inhibition of cellular proliferation and induction of apoptosis. Ponatinib also inhibits the proliferation of cell lines expressing other major clinically observed imatinib-resistant mutants of BCR-ABL. In an in vitro mutagenesis screen designed to characterize the resistance profile of ponatinib, no mutations in BCR-ABL were identified that alone could confer resistance to 40 nM ponatinib. Based on the promising preclinical activity profile of ponatinib, initial human clinical studies were conducted. The phase I study of ponatinib included patients diagnosed with a hematologic malignancy who relapsed or were refractory to standard care, or for whom no standard care was available. The primary objective was to determine the maximum tolerated dose (MTD) or a recommended dose of daily oral ponatinib. The phase II PACE study (Ponatinib Ph+ ALL and CML Evaluation) was initiated in September 2010 and is ongoing. The objective of this international, single-arm, open-label study is to establish the efficacy and safety of ponatinib in patients with refractory CML in CP, accelerated phase (AP) or blast phase (BP), or Ph+ ALL resistant or intolerant to dasatinib or nilotinib or with the T315I mutation. The primary endpoints are MCyR for CP-CML and major hematologic response (MaHR) for AP, BP, or Ph+ ALL. Findings from the phase I study of ponatinib show evidence of clinical antileukemic activity in patients with resistance to approved second-generation TKIs, dasatinib and nilotinib, including patients with the T315I mutation of BCR-ABL. Based on the phase I safety, pharmacokinetic (PK), pharmacodynamics (PD), and antileukemic activity, 45 mg was chosen as the recommended dose for further study in adults. In addition, data emerging from the pivotal, international, phase II study are promising, with a safety profile similar to that reported for the phase I study and early efficacy signals showing substantial antileukemic activity in heavily pretreated patients and those with refractory T315I, even after a short follow-up period. Results from these clinical studies, taken together with the strong preclinical data that characterize ponatinib, provide the rationale for investigation of ponatinib in Japanese patients with CML or Ph+ ALL.
Study Design	This will be a phase I/II, multi-center, open-label study of ponatinib in Japanese patients with CML who have experienced a failure of dasatinib or nilotinib therapy, or Ph+ ALL who have experienced a failure of prior TKIs because of resistance or intolerance. The study will consist of two components, a phase I component followed by a phase II component. The phase I component will be an open-label, dose-escalation study of two dose cohorts, 30 mg and 45 mg. At least 6 patients will be enrolled in each cohort to confirm the safety of the recommended dose (45 mg) of ponatinib in Japanese patients. The phase I component will employ a modified 3+3 design. After 6 patients complete their first cycle (1 cycle = 28 days) in a cohort and are evaluable for dose-limiting toxicities (DLTs), safety events, including any DLTs, will be reviewed in conference between the sponsor and the investigators. These discussions will occur prior to opening the next dose level. Patients who are not evaluable for DLTs will be replaced. Definitions of DLT and MTD, and rules for escalation to the next dose level are provided in Section 5.2. The second dose cohort (45 mg) will be enrolled once the 30 mg dose cohort is completed and all patients have received 1 full cycle (28 days) of ponatinib. Patients

	are expected to receive study drug over at least 1 cycle of study treatment, unless an unacceptable drug reaction or disease progression occurs. Patients who give their consent to remaining in the study for ongoing treatment may continue to receive additional cycles of study treatment as long as treatment is tolerated and disease progression has not occurred. The recommended phase II dose of ponatinib in Japanese patients will be determined (in conference between the investigator and sponsor) based on the evaluation of DLTs and safety in the 30 mg and 45 mg cohorts. Once the safety of the recommended dose of ponatinib in Japanese patients is confirmed, the phase II component will be initiated. This will be a phase II, single-arm, open-label study of ponatinib at the recommended dose (determined in phase I) in an additional 25 patients. An additional 3 patients will be dosed at 15 mg for collection of PK data. PK parameters at the 15-mg dose level will be modeled, along with the 30-mg and 45-mg dose levels for determination of PK linearity in Japanese patients. After PK samples collection on Day 1 and Day 8 in Cycle 1, patients at 15 mg will be allowed to dose-escalate to the recommended phase II dose (determined in the phase I component of the trial) at the investigators' discretion and will be assessed for efficacy and safety as phase II patients.
Study Objectives	Primary • Phase I: To examine the safety of the recommended dose of oral ponatinib in Japanese patients with CML who are resistant or intolerant to dasatinib or nilotinib, or with Ph+ ALL who are resistant or intolerant to prior TKIs • Phase II: To confirm the antileukemic activity of ponatinib in Japanese patients with CML who are resistant or intolerant to dasatinib or nilotinib, or with Ph+ ALL who are resistant or intolerant to prior TKIs, as evidenced by clinical responses, molecular responses, and clinical outcomes Secondary • To examine the PK of ponatinib in Japanese patients with CML who are resistant or intolerant to dasatinib or nilotinib, or with Ph+ ALL who are resistant or intolerant to prior TKIs • To describe potential pharmacogenomic markers of ponatinib antileukemic activity and to characterize the molecular status of patients
Study Endpoints	**Primary Endpoints** **Phase I:** Safety of the dose recommended in the previous foreign study of oral ponatinib in Japanese patients with CML who are resistant or intolerant to dasatinib or nilotinib, or with Ph+ ALL who are resistant or intolerant to prior TKIs **Phase II:** In the phase II component, the primary efficacy endpoints will be: • For CML patients in CP at study entry: MCyR, defined as complete cytogenetic response (CCyR) or partial cytogenetic response (PCyR) o CP patients in CCyR are not eligible for this study. • For CML patients in AP, BP, or Ph+ ALL at study entry: MaHR, defined as complete hematologic response (CHR) or no evidence of leukemia (NEL) o AP, BP, and Ph+ ALL patients in MaHR are not eligible for this study. **Secondary Endpoints** • For CML patients in CP: o Hematologic responses: CHR o Cytogenetic responses: confirmed MCyR o Molecular responses: major molecular response (MMR) • For CML patients in AP or BP or Ph+ ALL patients:

	○ Cytogenetic responses: CCyR, PCyR, confirmed MCyR ○ Molecular responses: MMR • For all patients: time to response (TTR), duration of response, progression-free survival (PFS), and OS **Exploratory Endpoints** • CCI • [redacted]
Diagnosis and Inclusion Criteria	1. Patients must have CML in any phase (CP, AP, or BP of any phenotype) or Ph+ ALL (defined in Sections 4.3 and 4.4). • All patients must have screening bone marrow (BM) cytogenetics with conventional banding performed within 42 days prior to beginning treatment. • Examination of at least 20 metaphases is required in patients in CP. If less than 20 metaphases are examined, the BM aspirate must be repeated. • Adequate BM aspirate with differential cell counts is required in patients with AP, BP, or Ph+ ALL. If an adequate aspirate is not obtained, the aspirate must be repeated. 2. Be previously treated with and resistant or intolerant to either dasatinib or nilotinib for CML or at least oe TKI for Ph+ ALL 2.1 Resistance is defined for CP-CML patients (CP at the time of initiation of dasatinib or nilotinib therapy) as follows. Patients must meet at least one criterion: a. Three months after the initiation of therapy: No cytogenetic response (>95% Ph+) or failure to achieve CHR b. Six months after the initiation of therapy: Less than a minor cytogenetic response (>65% Ph+) c. Twelve months after the initiation of therapy: Less than a PCyR (>35% Ph+) d. At any time after the initiation of therapy, the development of new BCR-ABL kinase domain mutations in the absence of CCyR (see Appendix A) e. At any time after the initiation of therapy, the development of new clonal evolution in the absence of CCyR f. At any time after the initiation of therapy, the loss of any cytogenetic response (from complete [0%], partial [1% to 35%], minor [36% to 65%], or minimal [66% to 95%] to a response at least 1 grade worse), confirmed in at least 2 consecutive analyses separated by at least 4 weeks g. At any time after the initiation of therapy, progression of disease (to AP or BP) 2.2 Resistance is defined for AP-CML patients (AP at the time of initiation of dasatinib or nilotinib therapy) as follows. Patients must meet at least 1 criterion: a. Three months after the initiation of therapy: failure to achieve an MaHR b. At any time after the initiation of therapy, the loss of an MaHR, confirmed in at least 2 consecutive analyses separated by at least 4 weeks c. At any time after the initiation of therapy, the development of new

BCR-ABL kinase domain mutations in the absence of an MaHR

2.3 Resistance is defined for BP-CML patients (BP at the time of initiation of dasatinib or nilotinib therapy) and Ph+ ALL patients as follows. Patients must meet at least 1 criterion:

a. One month after the initiation of therapy: failure to achieve an MaHR

b. At any time after the initiation of therapy, the loss of an MaHR, confirmed in at least 2 consecutive analyses separated by at least 1 week

c. At any time after the initiation of therapy, the development of new BCR-ABL kinase domain mutations in the absence of an MaHR

2.4 Intolerance is defined as:

a. Non-hematologic intolerance: Patients with grade 3 or 4 toxicity while on therapy, or with persistent grade 2 toxicity, unresponsive to optimal management, including dose adjustments (unless dose reduction is not considered in the best interest of the patient if response is already suboptimal), irrespective of the absence of a CCyR for CP patients or an MaHR for AP, BP, or Ph+ ALL patients

b. Hematologic intolerance: Patients with grade 3 or 4 toxicity (absolute neutrophil count [ANC] or platelets) while on therapy that is recurrent after dose reduction to the lowest doses recommended by the manufacturer, irrespective of the absence of a CCyR for CP patients or MaHR for AP, BP, or Ph+ ALL patients

NOTE: Although the above criteria define the failure of dasatinib or nilotinib therapy (mostly according to Baccarani et al., 2009), CML patients who have gone on to later-line therapy are eligible, having experienced a failure of dasatinib or nilotinib. Similarly, Ph+ ALL patients who have gone on to another TKI having experienced a failure of one prior TKI are eligible.

Patients must meet all of the remaining criteria to be eligible for the study:

3. Must be ≥18 years old
4. Provide written informed consent
5. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
6. Minimum life expectancy of 3 months or more
7. Adequate renal function defined as serum creatinine <1.5 × upper limit of normal (ULN) for institution
8. Adequate hepatic function defined as:
   a. Total bilirubin <1.5 × ULN
   b. Alanine aminotransferase (ALT [SGPT]) and aspartate aminotransferase (AST [SGOT]) <2.5 × ULN for institution (<5 × ULN if liver involvement with leukemia)
   c. Prothrombin time <1.5 × ULN
9. Normal pancreatic status defined as:
   a. Lipase ≤1.5 × ULN for institution
   b. Amylase ≤1.5 × ULN for institution
10. Normal QT interval corrected (Fridericia) (QTcF) interval on screening electrocardiogram (ECG) evaluation, defined as QTcF of ≤450 ms in males or ≤ 470 ms in females

	11. For females of childbearing potential, a negative pregnancy test must be documented prior to enrollment 12. Female and male patients who are fertile must agree to use an effective form of contraception with their sexual partners from enrollment through at least 4 months after the end of treatment 13. Ability to comply with study procedures, in the investigator's opinion
Exclusion Criteria	Patients are not eligible for participation in the study if they meet any of the following exclusion criteria: 1. Received TKI therapy within 7 days prior to receiving the first dose of ponatinib, or have not recovered (>grade 2 by National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 [NCI CTCAE v.4.0]) from adverse events (AEs) (except alopecia) due to agents previously administered 2. Received other therapies as follows: a. For CP and AP patients, 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 b. For BP patients, received chemotherapy within 7 days prior to the first dose of ponatinib; otherwise, 2a applies c. For Ph+ ALL patients, received corticosteroids within 24 hours before the first dose of ponatinib and other chemotherapy within 7 days prior to the first dose of ponatinib; otherwise, 2a applies 3. Underwent autologous or allogeneic stem cell transplant <60 days prior to receiving the first dose of ponatinib; any evidence of ongoing graft versus-host disease (GVHD) or GVHD requiring immunosuppressive therapy 4. Take medications that are known to be associated with Torsades de Pointes 5. Require concurrent treatment with immunosuppressive agents, other than corticosteroids prescribed for a short course of therapy 6. Have previously been treated with ponatinib 7. Patients with CP-CML are excluded if they are in CCyR 8. Patients with CP-CML are excluded if a baseline BM aspirate adequate for conventional cytogenetic analysis with 20 metaphases examined is not available. 9. Patients with AP-CML, BP-CML, or Ph+ ALL are excluded if they are in MaHR. 10. Patients with AP-CML, BP-CML, or Ph+ ALL are excluded if a baseline BM aspirate adequate for cell count and differential report is not available. Patients with a fibrotic marrow or dry tap that does not yield adequate cell counts for diagnosis are not evaluable for classification, and endpoints are not eligible. 11. 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. 12. Have significant, uncontrolled, or active cardiovascular disease, specifically including, but not restricted to: a. Myocardial infarction (MI) within 6 months prior to enrollment b. Unstable angina within 6 months prior to enrollment

	c. Congestive heart failure (CHF) within 6 months prior to enrollment d. History of clinically significant atrial arrhythmia as determined by the treating physician e. Any history of ventricular arrhythmia f. Cerebrovascular accident or transient ischemic attack (TIA) within 6 months prior to enrollment g. Any history of peripheral arterial occlusive disease requiring revascularization Any history of venous thromboembolism, including deep venous thrombosis or pulmonary embolism within 6 months prior to enrollment 13. Have a significant bleeding disorder unrelated to CML or Ph+ ALL 14. Have a history of pancreatitis or alcohol abuse 15. Have uncontrolled hypertriglyceridemia (triglycerides > 450 mg/dL) 16. Have malabsorption syndrome or other gastrointestinal illness that could affect absorption of orally administered ponatinib 17. Have been diagnosed with another primary malignancy within the past 3 years (except for non-melanoma skin cancer or cervical cancer in situ, or controlled prostate cancer, which are allowed within 3 years) 18. Are pregnant or lactating. Females and males who are fertile must agree to use an effective form of contraception from enrollment through at least 4 months after the end of treatment. Women who stopped breastfeeding before the initial dose of ponatinib are eligible for inclusion (forbidden period: the day of the initial ponatinib dose until 6 months from the last dosing). 19. Underwent 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 20. Have ongoing or active infection (including known history of human immunodeficiency virus [HIV], hepatitis B virus [HBV], or hepatitis C virus [HCV]). Testing for these viruses is not required in the absence of history. 21. Suffer from any condition or illness that, in the opinion of the investigator or the medical monitor, would compromise patient safety or interfere with the evaluation of the safety of the study drug 22. Have uncontrolled hypertension (diastolic blood pressure >90 mm Hg; systolic blood pressure >140 mm Hg). Patients with hypertension should be under treatment on study entry to effect blood pressure control.
Approximate Number of Patients	At least 34 patients with CML who are resistant or intolerant to dasatinib or nilotinib or Ph+ ALL who have failed prior TKIs because of resistance or intolerance will be enrolled (at least 12 patients in the phase I dose escalation component and 3 patients at 15 mg for determination of PK linearity). For the entire study (phase I and phase II combined), 17 CP CML patients and 17 CML patients other than CP-CML patients (AP-CML, BP-CML or Ph+ALL patients) are targeted (See Section 9.4).
Approximate Duration of Patient Participation	The duration of each patient's study participation will be up to 60 months, plus up to 3 weeks for screening and a 30-day follow-up period.
Approximate Duration of Study	The estimated duration of the study is approximately 72 months, including 12 months of enrollment and 60 months of follow-up. All patients who discontinue prematurely from the study will be followed for survival every 12 weeks ± 2 weeks starting after the last dose of study drug for up to 60 months from the initiation of therapy.

Approximate Number of Study Centers	Approximately 10-12 centers
Dosage and Administration	Ponatinib will be administered orally once daily at two dose levels, 30 mg and 45 mg, during the phase I dose escalation phase. Based on the recommended dose determined in the phase I component, 30 mg or 45 mg will be administered in the phase II expansion phase of the trial. For determination of PK, 3 additional patients will be given 15 mg orally once daily. **Dose Recommendations Based on Updated Data** Before Amendment 2 (Version 3.0), the recommended phase II dose of ponatinib for Japanese patients was determined to be 45 mg given once daily. However, an increase in the cumulative incidence of cardiovascular events has been noted in the phase II PACE trial over time (N=449). With a median follow up of 24 months, serious arterial thrombosis occurred in 11.8% of patients: cardiovascular events in 6.2% of patients, cerebrovascular events in 4.0% of patients, and peripheral vascular events in 3.6% of patients (some patients had more than one type of event). This compares to 8.0% after 11 months of follow up. At 24 months, serious venous occlusion occurred in 2.9% of patients, compared to 2.2% after 11 months of follow-up. Furthermore, 2 of 28 patients in AP24534-11-106 had cardiovascular events at a 45-mg dose. These results have prompted the need for reducing risk while maintaining the potential benefit of ponatinib. Recent multivariate analyses performed on data from the phase II PACE trial found significant relationships between dose intensity and the occurrence of ≥ grade 3 adverse events including vascular occlusion, thrombocytopenia, pancreatitis, neutropenia, rash, ALT, AST, lipase, and myelosuppression in CML patients treated with ponatinib. These data support the conclusion that lowering the daily dose of ponatinib can reduce the risk of serious adverse events and ischemia. Data from the phase II PACE trial also indicate that patients can achieve and maintain responses on lower doses. After a median follow-up of 24 months, 110/190 CP-CML patients with dose reductions had achieved MCyR, and over 90% maintained response (100/110). Of 87 patients who achieved response while on 45 mg, 44 had a dose reduction after response (14 patients had dose reductions to 15 mg). All 44 patients have maintained their response. Of 46 patients who achieved response while on 30 mg, 20 had a dose reduction after response. Of these, 18 maintained response; the 2 patients who lost response had a dose reduction to 15 mg that lasted only 1 day. To summarize, 62 of 64 patients who had a dose reduction after response maintained the response, including all 35 who had reduced doses for more than 90 days. This result suggests that for CP-CML patients, reduction to 15 mg once daily after achievement of a cytogenetic response can sustain that response. Among the patients with advanced disease (179 patients with AP-CML, BP-CML, or Ph+ ALL), 56 % achieved MaHR at the 45-mg dose. Of these, 19 had a dose reduction, and 9 of these 19 have lost response. Of the 10 who remain in response, 7 have had dose reductions lasting longer than 90 days: 3 patients with BP-CML (2 at 15 mg, 1 at 30 mg) and 4 patients with AP-CML (2 each at 15-mg and 30-mg doses). Fifteen patients achieved MaHR at 30 mg. Of these, 7 had a subsequent dose reduction, and 6 lost response. One patient with AP-CML remains in response, generally taking 15 mg every other day. Therefore, the following dose regimen is recommended: • For patients with CP-CML who achieve MCyR, consider reducing the ponatinib dose to 15 mg once daily, unless in the judgment of the investigator, the benefit/risk analysis taking into account the patient's CML characteristics, BCR-ABL mutation status, and the patient's cardiovascular risk justifies

	treatment with a higher dose. Escalate to 30 mg if response is lost. • All CP-CML patients currently on trial who have not yet achieved MCyR should consider ponatinib dose reduction to 30 mg/day unless, in the judgment of the investigator, the benefit/risk analysis taking into account the patient's CML characteristics, BCR-ABL mutation status, and the patient's cardiovascular risk justifies treatment with a higher or lower dose. • All Advanced phase (AP- or BP-CML or Ph+ALL) patients currently on trial should have their dose reduced to 30 mg/day unless, in the judgment of the investigator, the benefit/risk analysis taking into account the patient's CML characteristics, BCR-ABL mutation status, and the patient's cardiovascular risk justifies treatment with a higher dose. For all patients, document in the patient's chart and in the study drug administration page of the study case report form (CRF) the dosing changes based on the above recommendations or the justification not to change the patient from his or her current dose.
Concomitant Treatment	The following concurrent medications are prohibited: • Any other anticancer therapy including, but not limited to, chemotherapeutic agents, immunotherapy, biological response modifiers, radiotherapy, surgery, and/or systemic hormonal therapy. However, intrathecal therapy for CNS relapse in lymphoid BP or Ph+ ALL is allowed. NOTE: Patients with active CNS disease at study entry are excluded. • Use of any other investigational drug or device • Use of medications that are known to be associated with the development of Torsades de Pointes (see Appendix B) • Herbal preparations or related over-the-counter preparations containing herbal ingredients (eg, St. John's wort, black cohosh, Estroven) either during or within 2 weeks prior to the first dose of ponatinib • Elective surgery requiring in-patient care The following medications should be avoided, but are not prohibited: • Medications that are strong inhibitors or inducers of cytochrome P450 (CYP) 3A (see Appendix C) • Medications that prolong the QT interval. If such medications are necessary and used while a patient is on study, then additional (ECG monitoring should be performed as clinically indicated (see Appendix B).
Efficacy Evaluation	Hematologic response, cytogenetic response, and molecular response will be assessed according to standard criteria (see Appendix A).
Safety Evaluation	Safety will be assessed by routine physical and laboratory evaluations, ECGs, and AEs, and will be recorded, and the severity will be graded according to the NCI CTCAE v.4.0 (see Appendix D).
Pharmacokinetic Evaluation	Blood samples will be collected at specified time points to study the PK of ponatinib. Pharmacokinetic parameters such as time of maximum concentration (T_{max}), maximum plasma concentration (C_{max}), area under the curve (AUC), and elimination half-life ($t_{1/2}$) will be determined, where possible.
Other Assessments	Other assessments include CCI and survival.

Statistical Analysis	Descriptive statistics and analyses will be provided for each dose level, and for patients combined across dose levels, where applicable. Data from patients in the phase 2 expansion phase will be summarized together with data from patients in the dose escalation cohorts, as appropriate within disease group, with each disease type summarized separately (CP-CML, AP-CML, BP-CML, Ph+ALL), and with the advanced phases (AP-CML, BP-CML, and Ph+ALL) pooled. Descriptive statistics (such as means, medians, standard deviations, ranges for continuous data, and percentages for categorical data) will be used to summarize patient characteristics, treatment administration/compliance, efficacy, safety, and PK parameters. Data will also be displayed graphically, where appropriate. All efficacy analyses will include all patients in the treated population. **CP-CML Patients**: The primary analysis of the primary efficacy endpoint of MCyR will be performed using a 1-sided exact 95% confidence interval (CI) for the MCyR rate and will be based on the total number of CP-CML patients enrolled in the dose-escalation phase and expansion phase. Major cytogenetic response rate is defined as the proportion of patients who have achieved a CCyR or PCyR after initiation of study treatment. Patients entering the study already in PCyR must achieve a CCyR in order to be considered a success for the MCyR rate. **AP-CML, BP-CML, Ph+ ALL Patients**: Major hematologic response rate is defined as the proportion of patients who have achieved a confirmed CHR or NEL after initiation of study treatment. The primary analysis of the primary efficacy endpoint of MaHR will be performed using a 1-sided exact 95% CI for MaHR rate and will be based on the total number of patients enrolled in the dose-escalation phase and expansion phase for each group and combined across the disease groups (AP-CML, BP-CML and Ph+ ALL). All patients receiving at least 1 dose of study drug will be considered evaluable for safety.
Rationale for Number of Patients	Six patients will be enrolled at each dose level of 30 mg and 45 mg to allow for adequate assessment of tolerability and evidence of clinical activity. The number of patients at each dose level is consistent with phase I dose-finding studies. An additional 3 patients will be included at 15 mg for the purposes of PK sample collection during Cycle 1 in order to determine PK linearity in Japanese patients. These patients will be allowed to dose escalate to the recommended phase II dose (at the discretion of the investigator) and will be assessed for efficacy and safety as phase II patients. The phase II portion of the study will allow confirmation of the overall tolerability of ponatinib and an estimate of its antileukemic activity in Japanese patients. For the phase II component, combined data from phase I and phase II will be evaluated. It is assumed that a 40% efficacy rate (MCyR rate for CP-CML and MaHR rate for others) and a 10% uninteresting rate for both groups are set. Sixteen patients per group are needed to retain 80% power for testing, using a 5% 1-sided significance level. Assuming 1 ineligible patient per group would be included, 17 patients per group (total of 34 patients) will be enrolled.
Medical Institutions and Investigators	Medical institutions and investigators are shown in a separate pamphlet.
Study Administrative Structure	Study administrative structure (project manager, auditors, data management, biostatistics, etc.) is shown in a separate pamphlet.

Medical Specialist	Professor Tomoki Naoe, President, National Hospital Organization, Nagoya Medical Center

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LIST OF ABBREVIATIONS

Abbreviation	Term
ABL	Abelson
AE	adverse event
AESI	adverse event of special interest
ALL	acute lymphoblastic leukemia, also known as acute lymphocytic leukemia
ALT	alanine aminotransferase
AML	acute myelogenous leukemia, also known as acute myeloid leukemia
ANC	absolute neutrophil count
AP	accelerated phase
ARIAD	ARIAD Pharmaceuticals, Inc
AST	aspartate aminotransferase
AUC	area under the curve
β-HCG	beta-human chorionic gonadotropin
BCR	Breakpoint Cluster Region
BCR-ABL	Breakpoint Cluster Region-Abelson
BM	bone marrow
BP	blast phase
BUN	blood urea nitrogen
CBC	complete blood count
CCyR	complete cytogenetic response
CHF	congestive heart failure
CHR	complete hematologic response
CI	confidence interval
C_{max}	maximum plasma concentration
CML	chronic myelogenous leukemia, also known as chronic myeloid leukemia
CNS	central nervous system
CP	chronic phase
CTCAE	Common Terminology Criteria for Adverse Events
cTn	cardiac troponin
CYP	cytochrome P450
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EFS	event-free survival
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor

Abbreviation	Term
GVHD	graft versus-host disease
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICMJE	International Committee of Medical Journal Editors
INR	International Normalized Ratio
IRB	Institutional Review Board
IRIS	International Randomized Study of Interferon and ST1571
LBBB	left branch bundle block
LV	left ventricular
LVEF	left ventricular ejection fraction
MaHR	major hematologic response
MCyR	major cytogenetic response
MHLW	Ministry of Health, Labor, and Welfare (Japan)
MI	myocardial infarction
MMR	major molecular response
MRI	magnetic resonance image/imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network (United States)
NCI	National Cancer Institute (of the United States)
NEL	no evidence of leukemia
OS	overall survival
PACE	Ponatinib Ph+ ALL and CML Evaluation
PCR	polymerase chain reaction
PCyR	partial cytogenetic response
PD	pharmacodynamics
PFS	progression-free survival
Ph+	Philadelphia chromosome-positive
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PT	prothrombin time
PTT	partial thromboplastin time
QD	daily
QT	QT interval; a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc	heart rate-corrected QT interval (calculated)
QTcF	QT interval corrected (Fridericia)
R/I	resistant/intolerant
SAE	serious adverse event
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
$t_{1/2}$	terminal elimination half-life
TIA	transient ischemic attack
TKI	tyrosine kinase inhibitor
T_{max}	time to reach maximum plasma concentration

Abbreviation	Term
TTR	time to response
ULN	upper limit of normal
URL	upper reference limit
WBC	white blood cell

DEFINITIONS OF TERMS

Term	Definition
30 Days After End-of-Treatment	At 30 days after the end of treatment, a patient completes all post-treatment discontinuation assessments.
Active Study Period	The *active study period* for a patient begins with administration of the first dose of study drug and continues through 30 days following discontinuation of study drug.
Suspected Adverse Reaction	A *suspected adverse reaction* is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of study safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.
Clinically Significant	A clinical observation or laboratory result that leads to a new intervention or change in therapy is defined in the context of this study as *clinically significant*.
Cycle	For the purposes of this study, a *cycle* consists of 28 days.
End-of-Treatment	The end of treatment occurs when a patient receives final dose of study drug or discontinues taking study drug and completes the *end-of-treatment* assessments
End-of-Study	The *end-of-study* (completion) date is when all patients have completed all study visits or have otherwise discontinued from the study.
Enrolled Patient	An *enrolled patient* is a patient who has signed the informed consent form, completed all screening evaluations, and has received study drug.
Evaluable for Efficacy	Any eligible patient who receives study drug is considered *evaluable for efficacy* analyses.
Evaluable for Safety	Any patient who receives study drug is considered *evaluable for safety* analyses.
Follow-up Period	The *follow-up period* for a patient begins after the last completed assessment during the active study period and continues until patient contact discontinues.
Institutional Review Board	Throughout this document the term *Institutional Review Board* (IRB) refers to all appropriate properly constituted committees or boards recognized by the head of institute for approving clinical studies. These

Term	Definition
	include independent ethics committees (ECs) and IRBs.
On-Study Period	The *on-study period* for a patient begins with the signing of the informed consent form and concludes 30 days following the last dose of study drug.
Patient	Throughout this document the term *patient* refers to a patient in this clinical research study.
QTcF	For the purposes of this study, the corrected (Fridericia) QT interval is calculated using the following formula: *QTcF* = QT/(RR)1/3.
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); Ethical Guidelines for Clinical Research (Ministry of Health, Labor, and Welfare [MHLW] in Japan); Good Clinical Practice (GCP) Guidelines (MHLW); Japan Pharmaceuticals Affairs Law; the International Conference on Harmonisation Guideline for GCP; and the World Medical Association Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Patients).
Regulatory Agency	Throughout this document the term *regulatory agency* refers to all appropriate health and regulatory agencies. These may be international, national, or local and may include but not be limited to Ministry of Health, Labor, and Welfare (Japan), Pharmaceuticals and Medical Devices Agency (PMDA), and the Food and Drug Administration (FDA; United States).
Screening Period	The *screening period* for a patient begins when the informed consent form is signed and continues until the first dose of study drug is administered.
Sponsor	Throughout this document the term *sponsor* refers to all appropriate research departments within ARIAD Pharmaceuticals, Inc, or its designee.
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.
Study Start Date	The *study start date* is the date that the first patient signs the informed consent form.

1 INTRODUCTION

1.1 Background

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder that represents about 15% of adult leukemias (Deininger et al, 2000). The underlying cause of CML is the Breakpoint Cluster Region-Abelson (BCR-ABL) fusion oncoprotein, which results from a reciprocal (9;22) chromosomal translocation in hematopoietic stem cells. This chromosomal abnormality (Philadelphia chromosome-positive [Ph+]) is present in about 95% of all patients with CML, as well as about 40% of adult patients with Ph+ acute lymphoblastic leukemia (ALL). The translocation leads to the fusion of the BCR coding sequence with the tyrosine kinase coding region of ABL. This fusion event results in the constitutive activation of ABL kinase activity, which is both necessary and sufficient for induction of CML or ALL (Deininger et al, 2000).

Imatinib was the first small molecule tyrosine kinase inhibitor (TKI) approved by the Food and Drug Administration (FDA) (United States) to treat CML patients. At 8 years of follow-up, the pivotal study of imatinib (IRIS: International Randomized Study of Interferon and ST1571 trial) in newly diagnosed chronic phase (CP)-CML patients has reported 81% event-free survival (EFS) and 85% overall survival (OS) (Cortes et al, 2011). However, despite the success of imatinib, 45% of patients in the IRIS trial discontinued imatinib therapy. A substantial fraction of patients either initially fail to respond to imatinib or progress after a period of therapy. BCR-ABL point mutations in the ABL kinase domain that impair imatinib binding are the main cause of resistance to imatinib therapy, and account for approximately 40% to 50% of resistant cases of disease (Branford et al, 2003; Jabbour et al, 2006; Jones et al, 2009; Terasawa et al, 2010; O'Hare et al, 2011).

Second-generation small-molecule inhibitors, dasatinib and nilotinib, are more potent than imatinib and inhibit many, but not all, imatinib-resistant point mutants, as well as native BCR-ABL (Talpaz et al, 2006; Kantarjian et al, 2006). Dasatinib and nilotinib were approved in Japan in 2009. Both are approved for use in patients who have experienced a failure of imatinib therapy, based on phase II clinical trials, in which approximately 40% to 45% of CP-CML patients achieved major cytogenetic responses (MCyRs) (Pinilla-Ibarz et al, 2008; Kantarjian et al, 2007). However, the remainder of patients, many of whom carry resistance mutations, remained refractory. Of note, both dasatinib and nilotinib are ineffective against the uniformly resistant T315I BCR-ABL mutation, which represents 15% to 20% of all clinically observed mutations (O'Hare et al, 2007).

To address the problem of resistance to the first- and second-generation BCR-ABL TKIs, ARIAD Pharmaceuticals, Inc (ARIAD) has developed ponatinib. Ponatinib is a novel synthetic orally active TKI, specifically developed to inhibit BCR-ABL, the fusion protein that is the product of the Philadelphia chromosome in CML and in a subset of ALL. It potently inhibits the BCR-ABL protein, as well as mutated forms of the protein that arise in patients resistant to prior therapies with TKIs; for this reason, it is a pan-BCR-ABL inhibitor.

In vitro assays have demonstrated that ponatinib potently inhibits the enzymatic activity of the T315I ABL kinase domain, as well as that of the native (unmutated) enzyme. In leukemia cell lines expressing these BCR-ABL variants, ponatinib potently inhibited BCR-ABL signaling, leading to inhibition of cellular proliferation and induction of apoptosis. Ponatinib also inhibits

the proliferation of cell lines expressing other major clinically observed imatinib-resistant mutants of BCR-ABL. In an in vitro mutagenesis screen designed to characterize the resistance profile of ponatinib, no mutations in BCR-ABL were identified that alone could confer resistance to 40 nM ponatinib. Based on the promising preclinical activity profile of ponatinib, initial human clinical studies were conducted.

Phase I Clinical Study of Ponatinib

The phase I study of ponatinib included patients diagnosed with a hematologic malignancy who relapsed or were refractory to standard care, or for whom no standard care was available. The primary objective was to determine the maximum tolerated dose (MTD) or a recommended dose of daily oral ponatinib. Secondary objectives included safety and pharmacokinetics (PK) of ponatinib, along with characterization of antileukemic activity, pharmacodynamic (PD) activity, and potential pharmacogenomic markers of activity. Patients (≥18 years) were administered ponatinib orally once daily. Dosing began at 2 mg and extended up to 60 mg. Enrollment closed in October 2010. Data are presented through 22 July 2011.

In total, 81 patients (54% male) received ponatinib and were followed for a median duration of 377 (range 11 to 977) days; at the time of analysis, 35 (43%) patients were ongoing. Diagnoses included 60 CML (43 CP, 17 advanced), 5 Ph+ ALL, 12 acute myeloid leukemia (AML), and 4 other. Prior therapies in Ph+ patients included imatinib (97%), dasatinib (89%), nilotinib (55%); 94% experienced a failure of ≥2, and 63% experienced a failure of ≥3 prior TKIs; 51% experienced failure of imatinib, dasatinib, and nilotinib. At entry, 65% had BCR-ABL mutations, including 29% T315I and 11% F317L.

The maximum administered dose was 60 mg, at which point dose-limiting toxicities (DLTs) of increased amylase and increased lipase, concurrent with grade 2 pancreatitis were reported. Additional DLTs included rash, fatigue, and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation. All DLTs were reversible. Some patients were able to tolerate 60 mg and remain on study at this dose, but overall, 60 mg was declared to exceed the MTD. Based on this observation, as well as on PK, PD, and antileukemia activity, 45 mg was chosen as the recommended dose for further study in adults.

Ponatinib was found to have an acceptable safety profile at therapeutic dose levels. Constitutional symptoms were the most common drug-related adverse events (AEs) reported, including rash (30%), arthralgia (16%), fatigue (16%), headache (15%), nausea (15%), dermatitis acneiform (14%), dry skin (14%), myalgia (12%), and abdominal pain (10%). Elevated lipase (15%), pancreatitis (12%), hypertriglyceridemia (12%), and ALT increased (10%) were also observed. The most common treatment-related hematologic events were thrombocytopenia (27%), neutropenia (12%), and anemia (11%). Treatment-related serious adverse events (SAEs) were reported for 12 (15%) patients; the most common of which was pancreatitis (9%; grade 3: 3%). There were 10 deaths on study, none of which were treatment-related. Twelve patients (15%) discontinued due to AEs.

A subgroup analysis of the heart rate-corrected QT interval (QTc) of patients who received ponatinib 30 mg or higher revealed there was no significant effect of ponatinib on cardiac repolarization in this refractory population.

Of 43 evaluable CP-CML patients, 42 (98%) experienced a complete hematologic response (CHR) and 31 (72%) experienced a MCyR, including 27 (63%) complete cytogenetic responses

(CCyR). Of the 12 CP-CML T315I patients, 100% experienced a CHR and 11 (92%) a MCyR, including 9 CCyR (75%). The median duration of follow-up for CP-CML patients was 511 (range 51 to 977) days. Overall, 19/43 (44%) CP-CML evaluable patients achieved major molecular response (MMR), as did 8/12 (67%) CP-CML T315I patients. Responses were also observed in patients with other mutations and in refractory patients with no detectable mutations.

For 22 evaluable advanced CML (accelerated phase [AP]-CML, blast phase [BP]-CML) or Ph+ALL patients, 9 (41%) experienced a major hematologic response (MaHR) and 7 (32%) experienced an MCyR. Of this advanced group, 7 had T315I mutation, 2 (29%) of which had MaHR and MCyR.

In summary, the phase I data suggest that ponatinib has a tolerable safety profile in a population of patients with advanced hematologic malignancies. Substantial evidence of clinical antileukemic activity was observed in heavily pretreated patients, including refractory patients with the T315I mutation, patients with other mutations, and those with no mutations.

Phase II Clinical Study of Ponatinib

The phase II PACE study (Ponatinib Ph+ ALL and CML Evaluation) was initiated in September 2010. The objective of this international, single-arm, open-label study is to establish the efficacy and safety of ponatinib in patients with refractory CML in CP, AP, or BP, or Ph+ ALL, resistant or intolerant (R/I) to dasatinib or nilotinib, or with the T315I mutation. Patients received 45 mg ponatinib orally once daily in 1 of 6 cohorts: CP R/I; CP T315I; AP R/I; AP T315I; BP/ALL R/I; BP/ALL T315I. The primary endpoints are MCyR for CP-CML and MaHR for AP, BP, or Ph+ ALL. The study is ongoing; enrollment closed in September 2011.

As of 02 December 2011, 449 patients were enrolled and treated. Diagnoses included 207 CP R/I, 64 CP T315I, 60 AP R/I, 19 AP T315I, 48 BP/ALL R/I, and 46 BP/ALL T315I. Prior TKIs included imatinib only (4%), imatinib + dasatinib or nilotinib (39%), imatinib + dasatinib + nilotinib (53%); 94% experienced failure of ≥2 prior TKIs, and 59% experienced failure of ≥ 3 prior TKIs. Overall, 129 patients had the T315I mutation. Of the 315 R/I patients, 120 (38%) had non-T315I BCR-ABL mutations. At the time of analysis, 301 (67%) patients remained on therapy, and 148 (33%) discontinued (73 BP/ALL). The reasons for discontinuation included 50 (11%) progressive disease (35 BP/ALL), 35 (8%) AE, 16 (4%) death, and 35 (8%) other.

Substantial antileukemic activity was observed in this heavily pretreated population. For CP-CML, 116 (47%) of 248 evaluable patients had MCyR; response rates were 41% (79/191) for CP R/I and 65% (37/57) for CP T315I. For AP-CML, 37 (67%) of 55 evaluable patients had MaHR; response rates were 74% (31/42) for AP R/I and 46% (6/13) for AP T315I. For BP-CML and Ph+ ALL, 33 (37%) of 89 evaluable patients had MaHR; response rates were identical for BP/ALL R/I and BP/ALL T315I patients.

The most common treatment-related AEs (≥10% any grade) were rash (32%), thrombocytopenia (31%; 25% grade 3/4), dry skin (24%), abdominal pain (19%; 5% grade 3/4), headache (17%), fatigue (15%), neutropenia (15%; 14% grade 3/4), myalgia (14%), arthralgia (14%), lipase increased (14%), constipation (12%), anemia (12%; 7% grade 3/4), and nausea (11%). Based on this analysis of the pivotal phase II PACE trial, ponatinib has a safety profile nearly similar to that observed in phase I, but with a lower incidence of pancreatitis.

1.2 Rationale

Findings from the phase I study of ponatinib show evidence of clinical antileukemic activity in patients with resistance to approved second-generation TKIs, dasatinib and nilotinib, including patients with the T315I mutation of BCR-ABL. In addition, data emerging from the pivotal, international, phase II study are promising, with a safety profile similar to that reported for the phase I study, and early efficacy signals showing substantial antileukemic activity in heavily pretreated patients and those with refractory T315I, even after a short follow-up period. The results from these clinical studies, taken together with the strong preclinical data that characterize ponatinib provide the rationale for investigation of ponatinib in Japanese patients with CML or Ph+ ALL.

This is a phase I/II study of oral ponatinib. The study is a non-randomized, multi-center, dose-escalation study to evaluate and confirm the safety and tolerability of the recommended dose, PK, and efficacy of ponatinib in Japanese patients with CML who are resistant or intolerant to therapy with dasatinib or nilotinib, or with Ph+ ALL who are resistant or intolerant to therapy with TKIs. The study consists of two components, a phase I (dose-escalation) component followed by a phase II component.

The dose-escalation portion of the study is designed to ascertain, by clinical and PK criteria, the safety and antileukemic activity of doses of ponatinib that have been demonstrated to be safe and to possess antileukemic activity in phase I and phase II studies. In the initial phase 1 study of ponatinib (discussed in Section 1.1), the recommended dose was determined as 45 mg once daily. This study will start at a lower dose level (30 mg) and increase to a 45 mg dose level once safety is established. The recommended phase II dose of ponatinib for Japanese patients will be determined (in conference between the investigator and sponsor) based on the evaluation of dose-limiting toxicities (DLT) and safety in 30 mg and 45 mg cohorts.

Once the safety of the recommended dose of ponatinib in Japanese patients is confirmed, the phase II component will be initiated. This will be a phase II, single-arm, open-label study of ponatinib at the recommended dose (determined in phase I) in an additional 25 patients. The phase II portion of the study will allow for further characterization of ponatinib with regard to overall tolerability, and provide an estimate of its antileukemic activity in Japanese patients.

An additional 15-mg dose level will be included for the purposes of determining PK linearity in 3 Japanese patients. After collection of PK samples during Cycle 1, patients at 15 mg will be allowed to dose-escalate to the recommended phase II dose (determined in the phase I component of the trial) at the investigator's discretion, and will be assessed for efficacy and safety as phase II patients.

The study will be conducted in compliance with the protocol, the standards specified under Article 14, Paragraph 3 and Article 80-2 of the Japan Pharmaceuticals Affairs Law (PAL, 2006), and Good Clinical Practice (GCP).

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are:

- phase I component: examine the safety of the recommended dose of oral ponatinib in Japanese patients with CML who are resistant or intolerant to dasatinib or nilotinib, or with Ph+ ALL who are resistant or intolerant to prior TKIs
- phase II component: confirm the antileukemic activity of ponatinib in Japanese patients with CML who are resistant or intolerant to dasatinib or nilotinib, or with Ph+ ALL who are resistant or intolerant to prior TKIs, as evidenced by clinical responses, molecular responses, and clinical outcomes

2.2 Secondary Objectives

The secondary objectives of this study are:

- To examine the PK of ponatinib in Japanese patients with CML who are resistant or intolerant to dasatinib or nilotinib, or with Ph+ ALL who are resistant or intolerant to prior TKIs
- To describe potential pharmacogenomic markers of ponatinib antileukemic activity and to characterize the molecular status of patients

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This will be a phase I/II, multi-center, open-label study of ponatinib in Japanese patients with CML who have experienced failure of dasatinib or nilotinib therapy, or with Ph+ ALL who have experienced failure of prior TKIs because of resistance or intolerance.

The study will consist of 2 components, a phase I component followed by a phase II component. The phase I component will be an open-label, dose-escalation study of 2 dose cohorts, 30 mg and 45 mg. At least 6 patients will be enrolled in each cohort to confirm the safety of the recommended dose of ponatinib in Japanese patients.

The phase I component will employ a modified 3+3 design. After 6 patients complete their first cycle (1 cycle = 28 days) in a cohort and are evaluable for DLTs, safety events including any DLTs will be reviewed in conference between the sponsor and the investigators. These discussions will occur prior to opening the next dose level. Patients who are not evaluable for DLTs will be replaced (see Section 5.2). Definitions of DLT and MTD, and rules for escalation to the next dose level are provided in Section 5.2.

The second dose cohort (45 mg) will be enrolled once the 30 mg dose cohort is completed and all patients have received 1 full cycle (28 days) of ponatinib. Patients are expected to receive study drug over at least 1 cycle of study treatment, unless an unacceptable drug reaction or disease progression occurs. Patients who give their consent to remaining in the study for ongoing treatment may continue to receive additional cycles of study treatment for efficacy and safety assessment, as long as treatment is tolerated and disease progression has not occurred. The

recommended phase II dose of ponatinib in Japanese patients will be determined (in conference between the investigator and sponsor) based on the evaluation of DLTs and safety in the 30 mg and 45 mg cohorts.

Once the safety of the recommended dose of ponatinib in Japanese patients is confirmed, the phase II component will be initiated. This will be a phase II, single-arm, open-label study of ponatinib at the recommended dose (determined in phase I) in an additional 25 patients.

An additional 3 patients will be dosed at 15 mg for collection of PK data. PK parameters at the 15-mg dose level will be modeled, along with the 30-mg and 45-mg dose levels for determination of PK linearity in Japanese patients. After PK collection on Day 1 and Day 8 during Cycle 1, patients at 15 mg will be allowed to dose-escalate to the recommended phase II dose (determined in the phase I component of the trial), at the investigators' discretion, and be assessed for efficacy and safety as phase II patients.

For the entire study (phase I and phase II combined), approximately 15 CP-CML patients and approximately 8 patients each in AP-CML, BP-CML, and Ph+ALL are targeted, although the numbers may vary from these targets (see Section 9.4).

Disease assessments will be performed on a defined schedule in accordance with defined efficacy criteria specific to a patient's type of malignancy (see Appendix A).

Safety will be assessed by routine physical and laboratory evaluations, electrocardiograms (ECGs), and AEs, and will be recorded and the severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE v.4.0) (see Appendix D).

Each patient will be followed for up to 60 months after his/her first dose of ponatinib. Patients will be evaluated according to the Schedule of Events in Table 5 and Table 6.

3.2 Description of Treatment(s)

Ponatinib (15-mg, 30-mg, and 45-mg dose levels) will be administered orally once daily in 4-week cycles (1 cycle = 28 days).

3.3 Study Duration

It is expected to take approximately 12 months to complete enrollment in the study. The duration of each patient's study participation will be up to 60 months, plus 3 weeks for screening and a 30-day follow-up period. The duration of therapy will be determined by the patient's response and toxicity, and patients will remain on ponatinib if responding. Patients will be followed for response, progression, and survival up to 60 months following initiation of treatment. In addition, all patients who discontinue prematurely from the study will be followed for survival every 12 weeks ± 2 weeks starting after the last dose of study drug for up to 60 months from initiation of therapy.

3.4 Study or Site Termination

If the sponsor, investigator, medical monitor, or regulatory agencies discover conditions during the study that indicate that the study or site should be terminated, this action may be taken after appropriate consultation between the sponsor, investigator, and medical monitor.

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

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

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

4 SELECTION AND WITHDRAWAL OF SUBJECTS

At least 34 patients with CML who are resistant or intolerant to dasatinib or nilotinib, or with Ph+ ALL who have failed prior TKIs because of resistance or intolerance will be enrolled (at least 12 patients in the phase I dose-escalation component and 3 patients at 15 mg for determination of PK linearity). For the entire study (phase I and phase II combined), 17 CP CML patients and 17 CML patients other than CP-CML (AP-CML, BP-CML, or Ph+ALL) are targeted. Patients must meet the inclusion and exclusion criteria to be enrolled in the study.

4.1 Inclusion Criteria

1. Patients must have CML in any phase (CP, AP, or BP of any phenotype) or Ph+ ALL (defined in Sections 4.3 and 4.4).
   - All patients must have screening bone marrow (BM) cytogenetics with conventional banding performed within 42 days prior to beginning treatment.
   - Examination of at least 20 metaphases is required in patients in CP. If less than 20 metaphases are examined, the BM aspirate must be repeated.
   - Adequate BM aspirate with differential cell counts is required in patients with AP, BP, or Ph+ ALL. If an adequate aspirate is not obtained, the aspirate must be repeated.
2. Be previously treated with and resistant, or intolerant, to either dasatinib or nilotinib for CML or at least one TKI for Ph+ ALL:

   2.1 Resistance is defined for CP-CML patients (CP at the time of initiation of dasatinib or nilotinib therapy) as follows. Patients must meet at least one criterion.

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

   b. Six months after the initiation of therapy: Less than a minor cytogenetic response (>65% Ph+)

c. Twelve months after the initiation of therapy: Less than a partial cytogenetic response (PCyR) (>35% Ph+)

d. At any time after the initiation of therapy, the development of new BCR-ABL kinase domain mutations in the absence of CCyR (see Appendix A)

e. At any time after the initiation of therapy, the development of new clonal evolution in the absence of CCyR

f. At any time after the initiation of therapy, the loss of any cytogenetic response (from complete [0%], partial [1% to 35%], minor [36% to 65%], or minimal [66% to 95%] to a response at least 1 grade worse), confirmed in at least 2 consecutive analyses separated by at least 4 weeks

g. At any time after the initiation of therapy, progression of disease (to AP or BP)

2.2 Resistance is defined for AP-CML patients (AP at the time of initiation of dasatinib or nilotinib therapy) as follows. Patients must meet at least 1 criterion.

a. Three months after the initiation of therapy: failure to achieve an MaHR

b. At any time after the initiation of therapy, the loss of an MaHR, confirmed in at least 2 consecutive analyses separated by at least 4 weeks

c. At any time after the initiation of therapy, the development of new BCR-ABL kinase domain mutations in the absence of an MaHR

2.3 Resistance is defined for BP-CML patients (BP at the time of initiation of dasatinib or nilotinib therapy) and Ph+ ALL patients as follows. Patients must meet at least 1 criterion.

a. One month after the initiation of therapy: failure to achieve an MaHR

b. At any time after the initiation of therapy, the loss of an MaHR, confirmed in at least 2 consecutive analyses separated by at least 1 week

c. At any time after the initiation of therapy, the development of new BCR-ABL kinase domain mutations in the absence of an MaHR

2.4 Intolerance is defined as:

a. Non-hematologic intolerance: Patients with grade 3 or 4 toxicity while on therapy, or with persistent grade 2 toxicity, unresponsive to optimal management, including dose adjustments (unless dose reduction is not considered in the best interest of the patient if response is already suboptimal) irrespective of the absence of a CCyR for CP patients or an MaHR for AP, BP, or Ph+ ALL patients

b. Hematologic intolerance: Patients with grade 3 or 4 toxicity (absolute neutrophil count [ANC] or platelets) while on therapy that is recurrent after dose reduction to the lowest doses recommended by the manufacturer, irrespective of the absence of a CCyR for CP patients or MaHR for AP, BP, or Ph+ ALL patients

NOTE: Although the above criteria define failure after dasatinib or nilotinib (mostly according to Baccarani et al, 2009), CML patients who have gone on to later-line therapy are eligible, having experienced failure of dasatinib or nilotinib. Similarly, Ph+ ALL patients who have gone on to another TKI, having experienced failure of 1 prior TKI are eligible.

Patients must meet all of the remaining criteria to be eligible for the study:

3. Must be ≥ 18 years old
4. Provide written informed consent
5. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
6. Minimum life expectancy of 3 months or more
7. Adequate renal function defined as serum creatinine < 1.5 × upper limit of normal (ULN) for institution
8. Adequate hepatic function defined as:
   a. Total bilirubin < 1.5 × ULN
   b. ALT (SGPT) and AST (SGOT) < 2.5 × ULN for institution (< 5 × ULN if liver involvement with leukemia)
   c. Prothrombin time (PT) < 1.5 × ULN
9. Normal pancreatic status defined as:
   a. Lipase ≤ 1.5 × ULN for institution
   b. Amylase ≤ 1.5 × ULN for institution
10. Normal QT interval corrected (Fridericia) (QTcF) interval on screening ECG evaluation, defined as QTcF of ≤ 450 ms in males or ≤ 470 ms in females
11. For fertile females, a negative pregnancy test must be documented prior to enrollment
12. Female and male patients who are fertile must agree to use an effective form of contraception with their sexual partners from enrollment through at least 4 months after the end of treatment.
13. Ability to comply with study procedures, in the investigator's opinion

< Reasons for setting up the above inclusion criteria >

1. To specify the target patient population of CP, AP, and BP-CML and Ph+ALL
2. To define patients with CML who have experienced failure of dasatinib or nilotinib because of resistance or intolerance, or with Ph+ALL who have experienced failure of prior TKIs because of resistance or intolerance
3. 18 was set up as the age of patients who can fully understand this trial and follow the protocol.
4. To confirm that each patient participates in this trial with his/her own intention

5. ～6. To properly evaluate safety and efficacy of investigational drug

7. ～8. To select patients with substantially no marked damage in the function of liver, kidney, and hematological condition

9. To ensure the safety of patients against potential adverse reactions

10. Due to the uncertainty of QT/QTC prolongation by ponatinib

11. Due to the uncertainty of safety of ponatinib against fetus and infant

12. Due to the uncertainty of safety of ponatinib against fetus and infant, and due to insufficient data for the safety regarding spermatotoxicity

13. To secure safety of patients and to avoid patients who will not be able to obey the protocol.

4.2 Exclusion Criteria

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

1. Received TKI therapy within 7 days prior to receiving the first dose of ponatinib, or have not recovered (> grade 2 by NCI CTCAE v.4.0) from AEs (except alopecia) due to agents previously administered
2. Received other therapies as follows:
    a. For CP and AP patients, 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
    b. For BP patients, received chemotherapy within 7 days prior to the first dose of ponatinib; otherwise, 2a applies
    c. For Ph+ ALL patients, received corticosteroids within 24 hours before the first dose of ponatinib and other chemotherapy within 7 days prior to the first dose of ponatinib; otherwise, 2a applies
3. Underwent autologous or allogeneic stem cell transplant < 60 days prior to receiving the first dose of ponatinib; any evidence of ongoing graft versus-host disease (GVHD) or GVHD requiring immunosuppressive therapy
4. Take medications that are known to be associated with Torsades de Pointes
5. Require concurrent treatment with immunosuppressive agents, other than corticosteroids prescribed for a short course of therapy
6. Have previously been treated with ponatinib
7. Patients with CP-CML are excluded if they are in CCyR
8. Patients with CP-CML are excluded if a baseline BM aspirate, adequate for conventional cytogenetic analysis with 20 metaphases examined, is not available.
9. Patients with AP-CML, BP-CML, or Ph+ ALL are excluded if they are in MaHR.

10. Patients with AP-CML, BP-CML, or Ph+ ALL are excluded if a baseline BM aspirate adequate for cell count and differential report is not available. Patients with a fibrotic marrow or dry tap that does not yield adequate cell counts for diagnosis are not evaluable for classification, and endpoints are not eligible.
11. 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.
12. Have significant, uncontrolled, or active cardiovascular disease, specifically including, but not restricted to:
    a. Myocardial infarction (MI) within 6 months prior to enrollment
    b. Unstable angina within 6 months prior to enrollment
    c. Congestive heart failure (CHF) within 6 months prior to enrollment
    d. History of clinically significant atrial arrhythmia as determined by the treating physician
    e. Any history of ventricular arrhythmia
    f. Cerebrovascular accident or transient ischemic attack (TIA) within 6 months prior to enrollment
    g. Any history of peripheral arterial occlusive disease requiring revascularization
    h. Any history of venous thromboembolism, including deep vein thrombosis or pulmonary embolism within 6 months prior to enrollment
13. Have a significant bleeding disorder unrelated to CML or Ph+ ALL
14. Have a history of pancreatitis or alcohol abuse
15. Have uncontrolled hypertriglyceridemia (triglycerides > 450 mg/dL)
16. Have malabsorption syndrome or other gastrointestinal illness that could affect absorption of orally administered ponatinib
17. Have been diagnosed with another primary malignancy within the past 3 years (except for non-melanoma skin cancer, cervical cancer in situ, or controlled prostate cancer, which are allowed within 3 years)
18. Are pregnant or lactating. Females and males who are fertile must agree to an effective contraception from enrollment through at least 4 months after the end of treatment. Women who stopped breastfeeding before the initial dosing of ponatinib are eligible for inclusion (forbidden period: the day of the initial ponatinib dosing until 6 months from the last dosing).
19. Underwent 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

20. Have ongoing or active infection (including known history of human immunodeficiency virus [HIV], hepatitis B virus [HBV], or hepatitis C virus [HCV]). Testing for these viruses is not required in the absence of history.
21. Suffer from any condition or illness that, in the opinion of the investigator or the medical monitor, would compromise patient safety or interfere with the evaluation of the safety of the study drug
22. Have uncontrolled hypertension (diastolic blood pressure > 90 mm Hg; systolic blood pressure > 140 mm Hg). Patients with hypertension should be under treatment on study entry to effect blood pressure control.

< Reasons for setting up the above exclusion criteria >

1. ～2. To pay attention to safety of patients and to eliminate the effect to the evaluation of safety of investigational drug

3. ～5. To pay sufficient attention to safety of patients

6. To eliminate the effect to the evaluation of safety and efficacy of investigational drug

7. ～10. To properly evaluate the efficacy of investigational drug

11. To pay attention to safety of patients and to eliminate the effect to the evaluation of safety of investigational drug

12. To pay sufficient attention to safety of patients

13. ～15. To pay attention to safety of patients and to eliminate the effect to the evaluation of safety of investigational drug

16. To eliminate the effect to the evaluation of efficacy of investigational drug

17. To eliminate the effect to the evaluation of safety and efficacy of investigational drug

18. Due to the uncertainty of safety of ponatinib against fetus and infant

19. ～20. To pay sufficient attention to safety of patients

21. To pay attention to safety of patients and to eliminate the effect to the evaluation of safety of investigational drug

22. To pay attention to safety of patients and to eliminate the effect to the evaluation of safety of investigational drug

4.3 Classification of Chronic Myeloid Leukemia Patients

Patients with CML who enroll in the study will be classified according to Talpaz and colleagues in their studies of dasatinib (Talpaz et al, 2006). See Table 1 below.

Table 1 Chronic Myeloid Leukemia Phase Classification

CML Phase	Criteria
Chronic Phase (CP)	The following conditions are all observed: <15% blasts in peripheral blood or bone marrow <20% basophils in peripheral blood <30% blasts + promyelocytes in peripheral blood or bone marrow >100 x 10^9 platelets/L in peripheral blood No extramedullary disease other than hepatosplenomegaly
Accelerated Phase (AP)	At least 1 of 5 conditions (1-5) and 6 are observed. 1. >15% and < 30% blasts in peripheral blood or bone marrow 2. >20% basophils in peripheral blood or bone marrow 3.>30% blasts + promyelocytes in peripheral blood or bone marrow (but <30% blasts) 4. <100 x 10^9 platelets/L in peripheral blood unrelated to therapy 5. Cytogenetic, genetic evidence of clonal evolution 6. No extramedullary disease other than hepatosplenomegaly
Blast Phase (BP)	≥30% blasts in peripheral blood or bone marrow **or** Extramedullary disease other than hepatosplenomegaly

4.4 Philadelphia-Positive Acute Lymphoblastic Leukemia Patients

To be classified as having Ph+ ALL, patients must have >30% blasts in blood or BM at the time of diagnosis and no prior history of CML.

4.5 Subject Discontinuation

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(s) for withdrawal as thoroughly as possible. The reason(s) for termination must be clearly reported on the appropriate page of the patient's electronic case report form (eCRF).

If a patient is discontinued from the study for any reason, every effort must be made by the investigator 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.

Patients will be discontinued from further study drug administration in the event of any of the following:

- Intolerable toxicity, as determined by the investigator
- Progression of disease requiring an alternate therapy, in the opinion of the investigator
- Entry into another therapeutic clinical study or start of additional anticancer therapy
- Significant deviation from the protocol or eligibility criteria, in the opinion of the medical monitor or investigator

- Noncompliance with study or follow-up procedures
- Patient withdrawal of consent and decision to discontinue participation
- Patient with beta-human chorionic gonadotropin (β -HCG) test positive (pregnant)
- Termination of the study by the sponsor
- Any other reason that, in the opinion of the investigator, would justify removal of the patient from the study

Once a subject is taken off treatment, toxicity assessments will be performed at least every 4 weeks until all study-related toxicities resolve to baseline (or CTCAE grade ≤1), stabilize, or are considered to be chronic/irreversible.

All patients who are discontinued prematurely from the study will be followed for survival every 12 weeks ± 2 weeks starting after the last dose of study drug, for up to 60 months from initiation of therapy.

Patients who experience a DLT or drug-related AE and come off study during the first 28 days of participation will NOT be replaced for purposes of patient accrual. Any patient who is enrolled in the study but is discontinued for reasons other than a DLT or drug-related safety event prior to receiving at least 75% of scheduled doses in the first 28 days (Cycle 1) will be replaced.

5 STUDY TREATMENT(S)

5.1 Study Treatment(s)

Ponatinib tablets will be administered orally once daily at 2 dose levels, 30 mg and 45 mg, during the phase I dose-escalation phase. Based on the recommended dose determined in the phase I component, 30 mg or 45 mg will be administered in the phase II expansion phase of the trial. For determination of PK, 3 additional patients will be given 15 mg orally once daily.

5.1.1 Treatment Administration

Study drug will be administered only to eligible enrolled patients at participating centers. Patients do not need to continuously meet the eligibility criteria in order to continue on study drug.

Patients will take the prescribed number of tablets with water, with or without food, at approximately the same time each day. Patients who forget to take their dose should not make up the missed dose. Missed doses should be recorded in an appropriate source record (eg, hospital chart), patient diary card, and study drug administration eCRF. When possible, patients should take the study drug under observation during scheduled study visits to the clinic.

5.1.2 Dose Selection and Schedule

The starting dose for phase I is 30 mg (two 15-mg tablets) taken orally once daily. Once the safety of the 30-mg dose is confirmed, the second dose cohort will be enrolled and administered 45 mg (one 45-mg tablet) taken orally once daily. Based on the phase I results, 30 mg or 45 mg will be administered in phase II (expansion phase). In addition, a 15-mg dose level (one 15-mg tablet taken orally once daily) will be included (3 patients only) for determination of PK linearity.

Patients will begin taking study drug on Day 1 up to 60 months of treatment. Patients are expected to receive study drug over at least 1 cycle (28 days) of study treatment unless an unacceptable drug reaction or disease progression occurs. Patients who give their consent to the ongoing treatment in phase I portion may continue receiving the treatment in the following cycles.

5.2 Phase I Dose-Escalation Scheme

The dose-escalation scheme is described below. The investigators and sponsor will review safety data on an ongoing basis and make decisions regarding the advisability of continuing accrual or escalating to the next dose level cohort. The investigators and sponsor will consider the nature of the DLTs that occurred when making dose-escalation decisions.

Table 2 Phase I Dose-Escalation Decision Rules

Number of Patients with a DLT at a Given Dose Level	Escalation Decision Rule
0 out of 6	If 0 of 6 patients experience a DLT, the MTD has not been reached. Proceed to the next dose level or proceed to phase 2 (expansion phase) of the study as applicable.
≤1 out of 6	If 1 of 6 patients experiences a DLT, the MTD has not been reached. Proceed to the next dose level or proceed to phase 2 (expansion phase) of the study as applicable.
2 out of 6	If 2 of 6 patients experience a DLT, enroll an additional 6 patients (total 12). If none of the additional 6 patients experiences a DLT, the MTD has not been reached. Proceed to the next dose level or proceed to phase II (expansion phase) of the study, if applicable. If 1 of the additional 6 patients experiences a DLT, the MTD has been reached. If 2 or more of the additional 6 patients experience a DLT, the MTD has been exceeded.
>2 out of 6	If more than 2 of 6 patients experience a DLT, the MTD has been exceeded.

Definitions: DLT = dose-limiting toxicity; MTD = maximum tolerated dose.

If no patient or 1 out of the 6 patients has a DLT (defined below) during Cycle 1 of study treatment at the 30-mg dose, enrollment into the second dose level cohort (45 mg) will commence. Enrollment into the second dose level cohort will proceed only after all 6 evaluable patients have completed one full cycle (28 days) of study treatment. Patients who are not evaluable for DLTs will be replaced, ie, the sponsor may permit enrollment of additional patients in the cohort to ensure that there are 6 evaluable patients to complete the first cycle.

In the event that 2 of 6 patients experience a DLT, the cohort will be expanded to 12 patients. If no further DLTs are observed for 6 additional evaluable patients, and these patients complete a full cycle, enrollment to the next dose level will commence, or the study will continue into phase 2 (expansion phase) if this occurs at 45 mg. If 1 or more of the additional evaluable patients experience a DLT, the MTD will have been reached.

In the event that > 2 of 6 patients (or > 3 of 12 patients, if a dose level has been expanded) experience a DLT, the MTD has been reached.

5.2.1 Intra-patient Dose Escalation

During the dose-escalation phase I component of the trial, patients at 30 mg will continue at that dose while 45 mg is being evaluated. If 45 mg is selected as the recommended dose, patients will be allowed to escalate to 45 mg at the discretion of the investigator, provided that safety, such as dose reduction/drug withdrawal, must be assured before the dose escalation.

5.2.2 Replacements

Patients who experience a DLT or drug-related AE and come off study during the first 28 days of participation will NOT be replaced for purposes of patient accrual. Any patient who is enrolled in the study, but is discontinued for reasons other than a DLT or drug-related safety event prior to receiving at least 75% of scheduled doses in the first 28 days (Cycle 1) will be deemed not evaluable for DLTs and replaced.

5.2.3 Definition of Maximum Tolerated Dose and Dose Limiting Toxicity

The MTD is defined as the highest dose at which ≤ 1 of 6 (or ≤ 3 of 12, in the instance that a dose level has been expanded from 6 to 12 patients) evaluable patients experience a DLT. Evaluable patients must complete at least 75% of scheduled doses in Cycle 1. A cohort may be expanded to better define tolerability at a dosage level.

For the purposes of this protocol, the following AEs are considered to be DLTs that count for the determination of the MTD. Toxicity grades are defined in the NCI CTCAE v.4.0.

- Grade ≥ 3 non-hematologic, with the exception of medically controllable toxicities (eg, nausea, vomiting, fatigue, electrolyte disturbances, hypersensitivity reactions) lasting ≤ 3 days, but excluding alopecia
- Missed doses: > 25% of planned ponatinib doses over 28 days due to AEs in the first cycle
- Febrile neutropenia (the occurrence of an ANC < 500/μL concurrently with a temperature elevation of > 101 ºF), when neutropenia is not related to underlying acute leukemia, as defined below
- Hematologic toxicity: Dose-limiting hematologic toxicity is the occurrence of a grade 4 cytopenia > 28 days, not related to underlying disease according to the investigator. Bone marrow examination must demonstrate < 5% cellularity.

When there is ambiguity about whether an AE is related to the underlying disease as opposed to the study drug, the most conservative approach will be taken and the AE will be considered study drug-related.

5.2.4 Dose Recommendations Based on Updated Data

Before Amendment 2 (Version 3.0), the recommended phase II dose of ponatinib for Japanese patients was determined to be 45 mg given once daily. However, an increase in the cumulative incidence of cardiovascular events has been noted in the phase II PACE trial over time (N=449).

With a median follow up of 24 months, serious arterial thrombosis occurred in 11.8% of patients: cardiovascular events in 6.2% of patients, cerebrovascular events in 4.0% of patients, and peripheral vascular events in 3.6% of patients (some patients had more than one type of event). This compares to 8.0% after 11 months of follow up. At 24 months, serious venous occlusion occurred in 2.9% of patients, compared to 2.2% after 11 months of follow-up. Furthermore, 2 of 28 patients in AP24534-11-106 had cardiovascular events at a 45-mg dose. These results have prompted the need for reducing risk while maintaining the potential benefit of ponatinib.

Recent multivariate analyses performed on data from the phase II PACE trial found significant relationships between dose intensity and the occurrence of ≥grade 3 adverse events including vascular occlusion, thrombocytopenia, pancreatitis, neutropenia, rash, ALT, AST, lipase, and myelosuppression in CML patients treated with ponatinib. These data support the conclusion that lowering the daily dose of ponatinib can reduce the risk of serious adverse events and ischemia.

Data from the phase II PACE trial also indicate that patients can achieve and maintain responses on lower doses. After a median follow-up of 24 months, 110/190 CP-CML patients with dose reductions had achieved MCyR, and over 90% maintained response (100/110). Of 87 patients who achieved response while on 45 mg, 44 had a dose reduction after response (14 patients had dose reductions to 15 mg). All 44 patients have maintained their response. Of 46 patients who achieved response while on 30 mg, 20 had a dose reduction after response. Of these, 18 maintained response; the 2 patients who lost response had a dose reduction to 15 mg that lasted only 1 day. To summarize, 62 of 64 patients who had a dose reduction after response maintained the response, including all 35 who had reduced doses for more than 90 days. This result suggests that for CP-CML patients, reduction to 15 mg once daily after achievement of a cytogenetic response can sustain that response. Among the patients with advanced disease (179 patients with AP-CML, BP-CML, or Ph+ ALL), 56 achieved MaHR at the 45-mg dose. Of these, 19 had a dose reduction, and 9 of these 19 have lost response. Of the 10 who remain in response, 7 have had dose reductions lasting longer than 90 days: 3 patients with BP-CML (2 at 15 mg, 1 at 30 mg) and 4 patients with AP-CML (2 each at 15-mg and 30-mg doses). Fifteen patients achieved MaHR at 30 mg. Of these, 7 had a subsequent dose reduction, and 6 lost response. One patient with AP-CML remains in response, generally taking 15 mg every other day.

Therefore, the following dose regimen is recommended:

- For patients with CP-CML who achieve MCyR, consider reducing the ponatinib dose to 15 mg once daily, unless in the judgment of the investigator, the benefit/risk analysis taking into account the patient's CML characteristics, BCR-ABL mutation status, and the patient's cardiovascular risk justifies treatment with a higher dose. Escalate to 30 mg if response is lost.
- All CP-CML patients currently on trial who have not yet achieved MCyR should consider ponatinib dose reduction to 30 mg/day unless, in the judgment of the investigator, the benefit/risk analysis taking into account the patient's CML characteristics, BCR-ABL mutation status, and the patient's cardiovascular risk justifies treatment with a higher dose.
- All advanced phase (AP- or BP-CML or Ph+ALL) patients currently on trial should have their dose reduced to 30 mg/day unless, in the judgment of the investigator, the

benefit/risk analysis taking into account the patient's CML characteristics, BCR-ABL mutation status, and the patient's cardiovascular risk justifies treatment with a higher dose.

For all patients, document in the patient's chart and in the study drug administration page of the study case report form (CRF) the dosing changes based on the above recommendations or the justification not to change the patient from his or her current dose.

5.2.5 Management of Adverse Drug Reactions

Comprehensive assessments of any study drug-related AEs (adverse drug reactions) experienced by the patient will be performed throughout the study. Anticipated adverse drug reactions that may be experienced are described in the Clinical Investigator Brochure. The severity of the event, as well as clinical judgment, will be utilized to determine appropriate management of the patient for any AE experienced while participating in this study.

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

Dose Modification(s)

Phase I portion Cycle 1 is intended for DLT assessment and no dose change is planned. In phase I Cycle 1, and the phase II portion, dose delays and/or reductions will be implemented for patients who experience adverse drug reactions, as described below.

Table 3 describes guidelines for dose modification due to study-drug-related toxicity, graded according to NCI CTCAE v.4.0. These guidelines should be followed by clinical investigators; however, for an individual patient, dose interruptions, reductions, and treatment discontinuation should also be based on the clinical circumstance. Deviation from these guidelines must be documented and communicated with the sponsor. When the observed toxicity has resolved to ≤grade 1, the investigator may resume full dosing, if clinically indicated.

There will be no dose modifications for grade 1 or 2 non-hematologic toxicities (except for pancreatitis) attributable to the study drug that are manageable with supportive care or do not interfere with normal daily activities of the patient. In the event of a persistent grade 1 or 2 non-hematologic adverse drug reaction that is (1) intolerable due to clinical symptoms or interferes with normal daily activities, or (2) not controlled by optimal supportive care, the patient may be managed by dose delay or reduction as described in Table 3. There are no suggested dose modifications for grade 1 or 2 hematologic toxicities.

Guidelines for assessment and management of pancreatitis are also described in Table 3. Pancreatic toxicities may manifest as an isolated elevation of pancreatic enzymes (amylase, lipase) in the absence of symptoms, or by enzyme elevation coupled with clinical symptoms. In the latter case, imaging should be performed, but in the case of isolated enzyme elevations, it is optional. Note: NCI CTCAE v.4.0 in the Gastrointestinal disorders System Organ Class defines grade 2 pancreatitis as "enzyme elevation or radiologic findings only." Version 4.0 separately defines toxicity grades for isolated elevation of lipase or serum amylase, which are found in the Investigations section of the guidance. Refer to Table 3 for guidelines on management of pancreatitis with or without symptoms, and management of amylase/lipase elevations with or without symptoms.

In the event of a grade 3 or 4 AE attributed to study drug, the patient may be managed by dose reduction or delay as well. Guidelines are described in Table 3. Note that grade 3 or 4 myelosuppression might be attributable to disease rather than study drug. In this case, if dose reduction or delay is deemed necessary, it is allowed.

Study drug administration may be delayed for up to 28 days to allow for improvement (to grade 1 or screening) or resolution of the event. If longer delays are necessary, the case should be discussed with the medical monitor of the study. In the event toxicity is intolerable and not controlled, a decision may be made by the investigator to discontinue the patient from further study drug administration.

Table 3 Modifications for Adverse Events Attributable to Study Drug

Non-hematologic Toxicity	
Grade 1 or transient Grade 2	No intervention
Grade 2 Lasting >7 days with optimal care	When the initial dose is 45 mg: Hold ponatinib Resume at 45 mg after recovery to ≤grade 1 Recurrence at 45 mg: Hold ponatinib Resume at 30 mg after recovery to ≤grade 1 When the initial dose is 30 mg, or recurrence at 30 mg: Hold ponatinib Resume at 15 mg after recovery to ≤grade 1 When the initial dose is 15 mg, or recurrence at 15 mg: Hold ponatinib Resume at 15 mg every other day after recovery to ≤grade 1 Upon recurrence at 15 mg every other day: Consider discontinuing ponatinib
Grade 3 or 4	When the initial dose is 45 mg: Hold ponatinib Resume at 30 mg after recovery to ≤grade 1 When the initial dose is 30 mg, or recurrence at 30 mg: Hold ponatinib Resume at 15 mg after recovery to ≤grade 1 When the initial dose is 15 mg, or recurrence at 15 mg: Hold ponatinib Resume at 15 mg every other day after recovery to ≤grade 1 Upon recurrence at 15 mg every other day: Consider discontinuing ponatinib
Non-hematologic Toxicity	
Pancreatitis	
Grade 2 (elevated amylase or lipase only)	See amylase/lipase section below

Grade 2 (mild or moderate symptoms or radiologic findings)	When the initial dose is 45 mg: Hold ponatinib Perform ultrasound or abdominal CT scan with contrast If imaging is positive, continue holding ponatinib and repeat according to clinical care If imaging is negative, or after resolution by imaging, resume at 45 mg after recovery to ≤grade 1 Recurrence at 45 mg: Repeat above, except resume at 30 mg after recovery to ≤grade 1 When the initial dose is 30 mg, or recurrence at 30 mg: Repeat above, except resume at 15 mg after recovery to ≤grade 1 When the initial dose is 15 mg, or recurrence at 15 mg: Hold ponatinib Resume at 15 mg every other day after recovery to ≤grade 1 Upon recurrence at 15 mg every other day: Consider discontinuing ponatinib
Grade 3 (severe pain, vomiting, medication intervention indicated [eg, analgesia, nutritional support])	When the initial dose is 45 mg: Hold ponatinib Perform ultrasound or abdominal CT scan with contrast If imaging is positive, continue holding ponatinib and repeat according to clinical care If imaging is negative, or after resolution by imaging, resume at 30 mg after recovery to ≤grade 1 When the initial dose is 30 mg, or recurrence at 30 mg: Repeat above, except resume at 15 mg after recovery to ≤grade 1 When the initial dose is 15 mg, or recurrence at 15 mg: Repeat above, except resume at 15 mg every other day after recovery to ≤grade 1 Upon recurrence at 15 mg every other day: Consider discontinuing ponatinib
Grade 4	Hold ponatinib Consult sponsor

Amylase/Lipase	
Grade ≤2	No intervention, monitor closely
Grade 3 with no radiologic findings	When the initial dose is 45 mg: Hold ponatinib Resume at 45 mg after recovery to ≤grade 1 Recurrence at 45 mg: Hold ponatinib Resume at 30 mg after recovery to ≤grade 1 When the initial dose is 30 mg, or recurrence at 30 mg: Hold ponatinib Resume at 15 mg after recovery to ≤grade 1 When the initial dose is 15 mg, or recurrence at 15 mg: Hold ponatinib Resume at 15 mg every other day after recovery to ≤grade 1 Upon recurrence at 15 mg every other day: Consider discontinuing ponatinib
Grade 3 with radiologic findings or Grade 4	When the initial dose is 45 mg: Hold ponatinib Repeat imaging according to clinical care After resolution by imaging, resume at 30 mg after recovery to ≤grade 1 When the initial dose is 30 mg, or recurrence at 30 mg: Repeat above Resume at 15 mg after recovery to ≤grade 1 When the initial dose is 15 mg, or recurrence at 15 mg: Repeat above, except resume at 15 mg every other day after recovery to ≤grade 1 Upon recurrence at 15 mg every other day: Consider discontinuing ponatinib
LV dysfunction/CHF	
Grade 2 or 3	When the initial dose is 45 mg: Hold ponatinib Resume at 45 mg after recovery to ≤grade 1 Recurrence at 45 mg: Hold ponatinib Resume at 30 mg after recovery to ≤grade 1 When the initial dose is 30 mg, or recurrence at 30 mg: Hold ponatinib Resume at 15 mg after recovery to ≤grade 1 When the initial dose is 15 mg, or recurrence at 15 mg: Hold ponatinib Resume at 15 mg every other day after recovery to ≤grade 1 Upon recurrence at 15 mg every other day: Consider discontinuing ponatinib

Grade 4	Hold ponatinib Consult sponsor
Hematologic Toxicity	
Drug-related ANC/Platelets	
Grade 1 or 2	No dose adjustment
Grade 3 or 4	When the initial dose is 45 mg: Hold ponatinib Resume at 45 mg after recovery to ≤grade 1 Recurrence at 45 mg: Hold ponatinib Resume at 30 mg after recovery to ≤grade 1 When the initial dose is 30 mg, or recurrence at 30 mg; Hold ponatinib Resume at 15 mg after recovery to ≤grade 1 When the initial dose is 15 mg, or recurrence at 15 mg; Hold ponatinib Resume at 15 mg every other day after recovery to ≤grade 1 Upon recurrence at 15 mg every other day: Consider discontinuing ponatinib

Definitions: ANC = absolute neutrophil count; CHF = congestive heart failure; CT = computed tomography; LV = left ventricular.

5.2.6 Management of Selected Adverse Events

Dose reduction guidelines are outlined in Section 5.2.5. 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 study. Anticipated adverse drug reactions that may be experienced are described in the ponatinib Investigator Brochure. Event severity 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 medications, including those administered for therapy of symptoms considered to be associated with study drug administration, should be reported on the appropriate concomitant medication page of the patient's eCRF. The symptoms should be reported on the AE page.

Vascular Occlusion

Arterial and venous thrombosis and occlusions, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures have occurred in ponatinib-treated patients. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. Vascular occlusion adverse events were more frequent with increasing age and in patients with prior history of ischemia, hypertension, diabetes, or hyperlipidemia.

Arterial Occlusion and Thrombosis

Serious arterial thrombosis occurred in ponatinib-treated patients with some patients experiencing events of more than one type. Serious cardiovascular thrombosis events included myocardial infarction and coronary artery disease. Some patients developed congestive heart failure concurrent or subsequent to the myocardial ischemic event.

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

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

Monitor and aggressively treat factors that increase cardiovascular risk, such as hypertension, hypercholesterolemia, and hyperglycemia. Interrupt and consider discontinuation of study drug in patients who develop arterial thrombotic events. Any patient who experiences a serious adverse event of myocardial infarction, stroke, or urgent revascularization while on trial must be discontinued from the trial unless, for that individual patient, the investigator believes the potential benefits of ponatinib treatment are likely to exceed the risks of continued treatment.

Venous Thromboembolism

Venous thromboembolic events 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 thromboembolism.

Neuropathy

Peripheral and cranial neuropathy has occurred in ponatinib-treated patients. In clinical trials, peripheral neuropathies reported included the following: peripheral neuropathy, paresthesia, hypoesthesia, and hyperesthesia. Of the patients who developed neuropathy, many developed neuropathy during the first month of treatment. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, neuropathic discomfort, a burning sensation, neuropathic pain or weakness. Consider interrupting ponatinib and evaluate if suspected.

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 3.

Congestive Heart Failure 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.

Hypertension

Blood pressure should be monitored at each visit. Hypertension, as confirmed by at least 2 blood pressure measurements, should be graded according to CTCAE version 4.0, which defines hypertension as a disorder characterized by a pathological increase in blood pressure (a repeated elevation in blood pressure exceeding 140 mm Hg for systolic and exceeding 90 mm Hg for diastolic). For patients who develop hypertension or worsening hypertension during study treatment, aggressive antihypertensive medication should be initiated or optimized, at the discretion of the investigator, to achieve target blood pressure before interruption or dose reduction of study treatment. If hypertension is persistent, despite additional antihypertensive medications, or if grade 4 hypertension develops, dose interruption and reduction is recommended, according to dose modification guidelines for general non-hematologic AEs, as described in Section 5.2.5.

Ocular Toxicity

Serious ocular 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 cataract, glaucoma, iritis, iridocyclitis, and ulcerative keratitis. Conduct comprehensive eye exams at baseline and periodically during treatment.

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. The events are generally uncomplicated and reversible, and can be managed with a brief interruption of treatment and standard medical therapies. Almost all patients are able to continue with ponatinib treatment at the same or a reduced dose once the event has improved to grade 1 or resolved. Patients with low-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 3 for details.

Hemorrhage

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

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 rapid weight gain should be carefully investigated and appropriate treatment provided. Interrupt, reduce the dose of, or discontinue ponatinib, as outlined in Section 5.2.5.

Cardiac Arrhythmias

Supraventricular tachyarrhythmias and symptomatic bradyarrhythmias were reported in patients treated with ponatinib. Advise patients to report signs and symptoms of rapid heart rate (palpitations, dizziness) or those suggestive of slow heart rate (fainting, dizziness, or chest pain).

Myelosuppression

Myelosuppression is a common AE in patients with CML and occurs in CP patients as well as those in the accelerated and blast phases. The etiology for myelosuppression can be attributed to CML itself, the drugs used to treat CML, such as TKIs, or a combination of both. Neutropenia, anemia, and thrombocytopenia have all been commonly reported, either together or individually, in patients treated with ponatinib. While myelosuppression can occur any time during treatment, its onset most commonly occurs within the first month on treatment. These events can typically be managed with supportive care and, if felt to be treatment-related, either a reduction or interruption of treatment with ponatinib (Table 3) should occur. Rarely, one or more cytopenias can lead to permanent discontinuation of treatment. The use of hematopoietic growth factors such as granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) 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 place him/her at high risk of developing febrile neutropenia, primary prophylaxis use of colony-stimulating growth factors for the prevention or reduction of febrile neutropenia is recommended, according to the published National Comprehensive Cancer Network (NCCN) guidelines [NCCN Guidelines Version 1.2012 – Myeloid Growth Factors].

Tumor Lysis Syndrome

Clinically significant tumor lysis syndrome has been reported at initiation of treatment with TKIs in CML patients. The patients at risk of tumor lysis syndrome are those with high tumor/leukemic burden prior to treatment. These patients should be monitored closely, especially at the initiation of treatment. Appropriate tumor lysis syndrome precautions and prophylactic treatment (such as aggressive hydration with fluids and the initiation of allopurinol 600 mg/day or other appropriate treatments) should be initiated prior to the start of therapy for those at risk for tumor lysis syndrome. Rasburicase and other appropriate treatments for hyperuricemia or tumor lysis syndrome are permitted.

Rash and/or Pruritus

Skin rashes have been commonly reported to be associated with ponatinib. The vast majority of 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 non-pruritic, or 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.

Diarrhea, Nausea, and Vomiting

Diarrhea is a common side effect of ponatinib. The use of anti-diarrhea medications is permitted. Patients who experience ≥ grade 2 diarrhea may begin loperamide at its standard

treatment schedule (4 mg orally x 1, then 2 mg orally after each loose stool, up to a maximum of 16 mg/day).

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

Constitutional Symptoms/Joint Pain

Certain constitutional symptoms such as myalgia, arthralgia, headache, weakness, fatigue, asthenia, and low-grade fever have been 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 the 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 improved or resolved.

Compromised Wound Healing and Gastrointestinal Perforation

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

Prolonged QTcF

If a prolongation of QTcF is observed, it is important to perform serum electrolyte analysis (including potassium, calcium, and magnesium) and correct any significant abnormalities with supplements if below normal limits. It is also necessary to review all concomitant medications the patient is on and discontinue medications that are known or suspected to cause QT prolongation.

If no contributing reason is identified, and the reason for QTcF prolongation is believed to be due to study medication, dose interruption and reduction guidelines for general non-hematologic toxicities in Table 3 should be followed. Additionally, weekly ECG monitoring is recommended for 4 weeks upon resumption of study drug, then monthly for 6 months, and then every 3 months for the remainder of the study, or more frequently as clinically indicated.

5.3 Prior and Concomitant Treatment(s)/Therapy

Prior and concomitant medications will be recorded from 21 days prior to the start of study treatment, at study entry, and during the study (the 30-day Follow-up Visit after the last dose of the study drug) on the appropriate eCRF for each patient.

Reasonable efforts will be made to collect information on all prior cancer treatments received by the patient (chemotherapy, radiotherapy, immunotherapy, biologics, etc.). Prior therapy history consists of the specific oncologic regimens a patient has received, the dates of the regimen and the best response to the regimen, and the reason for failure of or intolerance to each regimen. Stem cell transplant or experimental therapy history will also be recorded.

All information must be obtained from the patient's medical chart and recorded on the patient's eCRF.

5.4 Permitted Treatment

All routine and appropriate supportive care (including blood products) will be provided 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 the patient.

Information on all concomitant medications, administered blood products, as well as interventions occurring during the study must be recorded on the 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 is permitted.
- Where appropriate, patients may be treated with hematopoietic growth factors (eg, colony-stimulating factors such as G-CSF or GM-CSF) per institutional guidelines.
- Where appropriate, hydroxyurea is permitted during the first cycle of ponatinib administration. Concomitant use must be discontinued by the end of the third week of ponatinib in patients with AP, BP, and Ph+ ALL, and by the end of the first cycle in all patients (including CP-CML), and is thereafter prohibited.

5.5 Prohibited Treatment(s)/Therapy

The following concurrent medications are prohibited:

- Any other anticancer therapy including, but not limited to, chemotherapeutic agents, immunotherapy, biological response modifiers, radiotherapy, surgery, and/or systemic hormonal therapy. However, intrathecal therapy for CNS relapse in lymphoid BP or Ph+ ALL is allowed. NOTE: Patients with active CNS disease at study entry are excluded.
- Use of any other investigational drug or device
- Use of medications that are known to be associated with the development of Torsades de Pointes (see Appendix B)
- Herbal preparations or related over-the-counter preparations containing herbal ingredients (eg, St. John's Wort, black cohosh, Estroven) within 2 weeks prior to the first dose of ponatinib
- Elective surgery requiring in-patient care

The following medications should be avoided, but are not prohibited:

- Medications that are potent inhibitors or inducers of cytochrome P450 (CYP)3A (see Appendix C) Medications that prolong the QT interval. If such medications are necessary and used while a patient is on study, additional ECG monitoring should be performed as clinically indicated (see Appendix B).

Once the patient has withdrawn from the study, concomitant medications and treatments should be recorded for 30 days after last dose or until all study drug-related toxicities have resolved, whichever is later.

5.6 Potential Drug Interactions

Based on in vitro studies, drug-drug interactions (DDIs) due to either CYP inhibition or induction by ponatinib are highly unlikely in clinical studies using the recommended daily dose of 45 mg. In vitro studies demonstrated that ponatinib is primarily metabolized by CYP3A. In view of this, a drug interaction study was performed with a strong CYP3A inhibitor in healthy subjects. Recent data from this ketoconazole–ponatinib drug-drug interaction (DDI) study indicate that maximum plasma concentration (C_{max}) and area under the curve (AUC) of ponatinib are approximately 47% and 78% higher (when dosed at 15 mg), respectively, in the presence of a strong CYP3A inhibitor, classifying ponatinib as a weak substrate of CYP3A (Clinical Study Report AP24534-11-103). Therefore, there is a possibility for a clinically relevant DDI if ponatinib is administered with strong inhibitors or inducers of CYP3A. Investigators should have patients discontinue strong inhibitors or inducers of CYP3A within 2 weeks of the first dose of ponatinib, if at all possible. If coadministration of ponatinib with a strong inhibitor of CYP3A is unavoidable, consider reduction of the ponatinib dose 1 level from the current (eg, 30 mg for a patient receiving 45 mg; 15 mg for a patient receiving 30 mg). For patients already receiving 15 mg daily due to a prior dose reduction, consider an alternative to the strong CYP3A inhibitor, or, if that is not possible, consult the sponsor. If patients are required to receive prolonged (>7 days) concomitant administration of an inducer of CYP3A with ponatinib, patient response should be monitored closely.

Medications that are associated with prolongation of the QT interval may interact with ponatinib and contribute to QT interval prolongation, which has the potential to contribute to ventricular arrhythmia. In addition, some medications associated with QT prolongation also interact with the CYP3A cytochrome, and an effect on the QT interval might thus be exacerbated. Concomitant administration of medications that are associated with a risk for Torsades de Pointes are prohibited (see Appendix B). Medications that otherwise prolong the QT interval should be avoided (see Appendix A).

A list of strong inhibitors or inducers of CYP3A is identified in Appendix C.

5.7 Phototoxicity Study

In a phototoxicity study of ponatinib in eyes and skins of pigmented rats, skin inflammation, dermal reaction on the darkly pigmented skin site, and ocular findings were noted. Therefore, the phototoxic properties of ponatinib were demonstrated, and the investigator should warn patients to protect their eyes and skin from direct sunlight exposure.

5.8 Treatment Compliance

Patients will be provided a diary card or equivalent where the date of ponatinib administration will be recorded. Any missing doses should be recorded in an appropriate source record (eg, hospital chart), patient diary card, and study drug administration eCRF. Training of patients should be documented in the appropriate source record (eg, clinic chart). When possible, patients should take the study drug under observation during scheduled study visits to the clinic. The Investigator is responsible for ensuring that the patient diary card(s) are accounted for and noted in the source documentation.

5.9 Treatment(s) Supply

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

5.9.1 Formulation, Packaging, and Labeling

Ponatinib drug product is manufactured as tablets. Each tablet contains either 15 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).

Ponatinib product is provided as 60 tablets of 15 mg in a bottle and 30 tablets of 45 mg in a bottle of a white density polyethylene (6.5 cm tall, 3.5 cm diameter, and 30 cc volume).

Container labels will bear the appropriate label text, as required by the J-GCP and the Japanese Regulatory Agency. J-GCP requires the following description on the label:

1). For Clinical Trial Use Only

2). Name and address of sponsor (ARIAD) &
Name and address of ICCC [redacted]

3). Chemical name or drug code (AP24534 or ponatinib)

4). Batch Number

5). Storage condition, expiring date, and other necessary information.

5.9.2 Preparation and Dispensing

The study pharmacist or designee at the site will be responsible for handling and dispensing study drug, and completing associated documentary paperwork. Supplies are shipped to the investigative site at appropriate intervals, depending on patient accrual. The site must use an appropriate dispensing log/accountability form provided by the sponsor, or an acceptable substitute approved by the sponsor. Each time study medication is dispensed for a patient, the following information must be recorded: the patient's initials, the patient's study number, 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.

5.9.3 Treatment(s) Storage and Accountability

The recommended storage condition for ponatinib is controlled at 10°C – 30°C.

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

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

No other utilization of ponatinib intended for use in this study is authorized by the sponsor. The sponsor will be responsible for the appropriate handling and disposition of residual study drug.

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

The sponsor (ICCC) should prepare the records of delivery and withdrawal of the test drug and records of disposition of residual test drug.

6 EFFICACY AND SAFETY ASSESSMENTS

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

6.1 Efficacy Assessments

Patients will be assessed for hematologic response, cytogenetic response, and molecular response every 2-3 cycles, according to criteria established and published for specific hematologic malignancies (Talpaz et al, 2006; O'Brien et al, 2003; Kantarjian et al, 2010, described in Appendix A). All patients will be followed for up to 60 months after the first dose of ponatinib.

6.1.1 Bone Marrow Aspirate and Cytogenetics

BM aspirate results must list the components required for assessing patient response. Results of any BM aspirate or biopsy, whether scheduled or unscheduled, should be recorded in the patient's eCRF. All BM examinations must include blast count and cytogenetic assessment by conventional banding.

The BM aspirate, with or without an optional biopsy, must occur within 42 days prior to the first dose of ponatinib and ± 7 days of the subsequent scheduled assessments. Biopsy and aspirate results must list the components required for assessing patient response, as delineated in Appendix A. Bone marrow examination must include cytogenetic assessment by conventional banding. Cytogenetic assessment requires examination of at least 20 metaphases. If less than 20 metaphases are examined, the BM aspirate must be repeated.

BM aspirate is required every 3 months for CP patients, at the end of Cycle 1 and Cycle 2, and then every 2 months for AP, BP, and Ph+ ALL patients. A BM aspirate is performed at the End-of-Treatment Visit if it has been ≥ 12 weeks for CP and ≥ 8 weeks for AP or BP or Ph+ ALL since the last BM aspirate. Bone marrow aspirates and biopsies may be performed at other times when clinically indicated.

6.1.2 BCR-ABL Molecular Response Assessment

A quantitative real-time polymerase chain reaction (PCR) assay will be used to measure BCR-ABL transcript levels in peripheral blood samples collected from all patients, and in BM samples collected from BP and Ph+ ALL patients. Samples must be collected at screening, during the treatment period at the same time as BM aspirates (ie, at least every 3 months for CP and at least every 2 months for AP, BP, and Ph+ ALL), and at the End-of-Treatment Visit. This

test quantifies the molecular response to therapy and will be reported to the participating investigator.

6.2 Safety Assessments

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

6.2.1 Adverse Events

Type, incidence, severity (graded in accordance with the NCI CTCAE v.4.0), timing, seriousness and relatedness, outcome, action taken with study drug, and treatment will be assessed and documented by the investigator throughout the study (see Section 8).

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

6.2.2 Vital Signs

Vital signs include temperature, pulse rate, respiratory rate, and blood pressure (when patient is seated). Height and weight are required only at screening.

6.2.3 Physical Examination

All physical examinations should address the presence or absence of hepatosplenomegaly and ECOG performance status. The extent of the physical examination should be consistent with the medical history and the patient's underlying disease. In patients with extramedullary involvement in AP, BP, or Ph+ ALL, the site(s) of involvement must be assessed at screening and in subsequent directed examinations defined in the protocol.

A complete physical examination (including comprehensive eye exams at baseline and periodically during treatment) will be performed at screening, on Cycle 1 Day 1 prior to the first administration of study drug, and at the End-of-Treatment Visit. Physical examinations at other time points may be directed to relevant findings in the patient. The Follow-up Visit physical examination may be directed to any relevant findings. ECOG status must be assessed during all physical examinations.

6.2.4 Clinical Laboratory Safety Assessments

Complete blood count (CBC) with differential, and PT and partial thromboplastin time (PTT) will be performed to assess patient safety, as well as hematologic response. Serum chemistry tests and pregnancy tests will be performed to assess patient safety. The following clinical laboratory safety assessments will be performed:

Complete Blood Count with Differential

Complete blood count with differential is defined as peripheral blood total white blood cell (WBC) count, hemoglobin, hematocrit, platelet count, ANC, and WBC differential reported individually for each cell type, including immature cells such as metamyelocytes, promyelocytes, and blasts, when present.

Serum Chemistry, Including Amylase and Lipase

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), glucose (including fasting glucose levels), albumin, creatinine, total bilirubin (direct and indirect), AST (SGOT), ALT (SGPT), alkaline phosphatase, magnesium, phosphorous, calcium, amylase, and lipase.

Serum Triglycerides

The fasting or non-fasting serum triglyceride level must be collected during screening (including fasting total and LDL cholesterol levels). If a patient is ineligible based on a non-fasting level, the test may be repeated with a fasting level to determine eligibility.

Prothrombin Time and Partial Thromboplastin Time

A peripheral blood sample will be collected during screening to measure PT and PTT. The PT may be expressed as an International Normalized Ratio (INR) or in seconds.

Pregnancy Test

A pregnancy test must be performed on fertile females. The pregnancy test must be a β-HCG test, and either urine or serum can be used. The test must be known to be negative prior to study drug administration and must be performed within 7 days prior to the first study drug administration. Women of childbearing potential at study start must also complete the pregnancy test at the End-of-Treatment Visit.

Women who are not of childbearing potential (status post-hysterectomy, status post-bilateral oophorectomy, or post-menopausal [defined as amenorrhea for at least 12 months, except those with chemical menopause diagnosed by an investigator]) do not need to have the test performed.

Thyroid function test (T3, T4, and TSH)

Thyroid function test will measure the levels of TSH, free T3 and free T4. The test will be performed at screening and Day 1 of Cycle 3.

6.2.5 Electrocardiogram

All ECGs must be 12-lead. The screening ECG must be performed within the 21-day screening window prior to study drug administration. For consistency, the QTcF method must be used for all calculations of QTc intervals, and the QTcF interval must be normal on screening as specified in the eligibility criteria (Section 4). If other medications known to prolong the QTcF interval are used while a patient is on study, additional ECG monitoring should be performed as clinically indicated.

6.2.6 Echocardiogram

An echocardiogram (ECHO) for assessment of left ventricular ejection fraction (LVEF) must be performed within the 21-day screening window. An ECHO should be performed at the end of Cycle 3 only if clinically indicated, and at the End-of-Treatment or Follow-up Visit only if abnormality develops during study.

6.3 Other Assessments

6.3.1 Additional Disease Assessments

Additional examination, laboratory studies, or imaging must be performed as appropriate to fully assess disease status. This may include documentation of hepatosplenomegaly or, in patients with extramedullary involvement, imaging the site(s) of involvement. The sites of involvement must be assessed at screening and in subsequent disease evaluations with appropriate laboratory tests or procedures.

6.3.2 BCR-ABL Mutation Testing

CCI [redacted]

6.3.3 Molecular Genetic Assessment

CCI [redacted]

6.3.4 Survival

All patients should be followed-up for survival every 12 weeks ± 2 weeks starting after the last dose of study drug for up to 60 months from initiation of therapy. These data do not need to be obtained during a visit, and phone contact is acceptable.

6.4 Pharmacokinetics

Blood samples will be collected at specified time points to study the PK of ponatinib. Pharmacokinetic parameters such as time of maximum concentration (T_{max}), C_{max}, AUC, and elimination half-life ($t_{1/2}$) will be determined where possible.

During both Cycle 1 and Cycle 2, blood samples will be collected immediately prior to the first dose (time 0), and 0.5, 1, 2, 4, 6, 8, and 24 hours after the first dose. The 24-hour sample will be collected prior to dosing on Day 2 for both cycles. Blood samples will also be collected prior to dosing on Cycle 1 Days 8, 15, and 22. An additional sample will be collected for AP, BP, and Ph+ ALL patients prior to dosing on Cycle 1 Day 28.

For the Phase II portion patients, PK samples will not be collected.

Regarding PK sample collection for patients who will be given 15 mg ponatinib daily in order to investigate PK linearity in Japanese patients, sampling time will be 0 (just before administration), 0.5, 1, 2, 4, 6, 8, and 24 hours after intake on Day 1 and Day 8 in Cycle 1, respectively.

7 STUDY PROCEDURES

Table 4 illustrates the planned flow of clinical study procedures. Concomitant treatments and AEs will be collected throughout the study.

Table 4 Study Flow Chart

<table>
<tr><td colspan="4">On-Study Period</td><td rowspan="2">Follow-Up Period</td></tr>
<tr><td>Screening Period</td><td colspan="3">Active Study Period</td></tr>
<tr><td rowspan="2">The screening period for a patient begins when the informed consent form is signed and continues until the first dose of study drug is administered.</td><td>Cycle 1</td><td>End of Treatment</td><td>30 Days After End of Treatment</td><td rowspan="2">The follow-up period for a patient begins after the last completed assessment during the active study period and continues until patient contact discontinues.</td></tr>
<tr><td>Patient receives first dose of study drug and is then considered an enrolled patient</td><td>Patient continues to receive study drug and/or undergo study procedures/ assessments as described in the protocol</td><td>Patient receives final dose of study drug or discontinues taking study drug and completes end-of-treatment assessments</td><td>Patient completes all post-treatment discontinuation assessments</td></tr>
</table>

In addition, in the phase I portion, before initiating Cycle 2, patients should be checked for their willingness to continue receiving treatment, and consent must be obtained.

The "on-study period" begins with signing the informed consent form and ends approximately 30 days following the last dose of study drug. The "active study period" begins with administration of the first dose of study drug and continues through approximately 30 days following discontinuation of study drug (ie, at the follow-up visit). The "follow-up period" (to collect survival data) begins after the last dose of study drug and continues for up to 60 months from initiation of therapy.

The Schedule of Events for the safety and efficacy assessments to be performed at each visit is provided in Table 5 (CP patients) and Table 6 (AP, BP, and Ph+ ALL patients).

Table 5 Schedule of Events for Chronic Phase Patients

Cycle (1 cycle = 28 days)	Active Study Period: Screening	Cycle 1				Cycle 2		Cycle 3			Cycles 4 to 13	End of Cycles 6, 9, 12	End of Every Third Cycle (15 to 60)	End-of-Treatment Visit[1]	Follow-up Visit[1]	Survival Follow-up[2]
Day	**-21 to 1**	**1**	**8**	**15**	**22**	**1**	**15**	**1**	**15**	**28**	**1**	**28**	**28**			
Procedure																
Informed Consent	X					X[14]										
Medical/Surgical History & Demographics[3]	X															
Cancer Diagnosis & Prior Cancer Therapy[4]	X															
BCR-ABL Mutation History	X															
Vital Signs[5]	X	X		X		X		X			X		X	X	X	
Physical Exam including Hepato-splenomegaly & ECOG Performance Status[6]	X	X		X		X		X			X		X	X	X	
Complete Blood Count with Differential	X	X	X	X	X	X	X	X	X		X		X	X	X	
Serum Chemistry[15], Amylase, Lipase	X	X		X		X	X	X	X		X		X	X	X	
Thyroid Function Test[7]	X							X								
Serum Triglycerides[8]	X															
PT & PTT	X															
Pregnancy Test (if applicable)	X													X		
12- lead Electrocardiogram	X	X				X				X				X		
Echocardiogram[9]	(X)									(X)				(X)	(X)	
Adverse Events									Throughout study							
Concomitant Medications									Throughout study							
Response Assessment																
Bone Marrow Aspirate & Cytogenetic Response[10]	X									X		X	X	X		
Molecular Response[11]	X									X		X	X	X		
Additional Disease Assessments[12]	X									X		X	X			
Exploratory Tests																
CCI																
CCI																
Pharmacokinetics																
PK Sampling[13]		X	X	X	X	X										
Survival Follow-Up																
Survival[2]																X

See footnotes after Table 6.

Table 6 Schedule of Events for Accelerated Phase, Blast Phase, and Ph+ ALL Patients

Cycle (1 cycle = 28 days)	Screening	Active Study Period: Cycle 1					Cycle 2			Cycle 3			Cycles 4 to 26		End of Even Cycles 4 to 60	End-of-Treatment Visit[1]	Follow-up Visit[1]	Survival Follow-up[2]
Day	**-21 to 1**	**1**	**8**	**15**	**22**	**28**	**1**	**15**	**28**	**1**	**15**	**28**	**1**	**15**	**28**			
Procedure																		
Informed Consent	X						X[14]											
Medical/Surgical History & Demographics[3]	X																	
Cancer Diagnosis & Prior Cancer Therapy[4]	X																	
BCR-ABL Mutation History	X																	
Vital Signs[5]	X	X		X			X			X			X		X	X	X	
Physical Exam including Hepatosplenomegaly & ECOG Performance Status[6]	X	X		X			X			X			X		X	X	X	
Complete Blood Count with Differential	X	X	X	X	X		X	X		X	X		X	X	X	X	X	
Serum Chemistry[15], Amylase, Lipase	X	X		X			X	X		X			X		X	X	X	
Thyroid Function Test[7]	X									X								
Serum Triglycerides[8]	X																	
PT & PTT	X																	
Pregnancy Test (if applicable)	X															X		
12- lead Electrocardiogram	X	X					X					X				X		
Echocardiogram[9]	(X)											(X)				(X)	(X)	
Adverse Events								Throughout study										
Concomitant Medications								Throughout study										
Response Assessment																		
Bone Marrow Aspirate & Cytogenetic Response[10]	X					X			X						X	X		
Molecular Response[11]	X								X						X	X		
Additional Disease Assessments[12]	X								X						X			
Exploratory Tests																		
CCI																		
CCI																		
Pharmacokinetics																		
PK Sampling[13]		X	X	X	X	X	X											
Survival Follow-Up																		
Survival[2]																		X

See footnotes on following pages.

Definitions: AP = accelerated phase; BCR-ABL= Breakpoint Cluster Region-Abelson; BM = bone marrow; BP = blast phase; ECG = electrocardiogram; CHF = congestive heart failure; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; MI = myocardial infarction; Ph+ ALL = Philadelphia chromosome positive acute lymphoblastic leukemia; PK = pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time; TIA = transient ischemic attack; WBC = white blood cell.

Footnotes for Schedule of Events Table 5 and Table 6.

1. 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. The Follow-up Visit will be conducted 30 days (± 7 days) after the last dose of study drug.
2. Survival data should be collected every 12 weeks ± 2 weeks starting after the last dose of study drug for up to 60 months from the initiation of therapy.
3. Medical and surgical history and demographic information will be recorded. Medical and surgical history includes diagnoses, therapies, medical and surgical treatments, and current medications, and must include any history of ischemic heart disease (including angina, myocardial infarction [MI], acute coronary syndrome, and/or coronary revascularization procedures), valvular heart disease, CHF, arrhythmias, myocarditis, peripheral arterial occlusive disease (including claudication, distal extremity amputation, angioplasty, and/or revascularization procedure), stroke (including TIA, cerebral atherosclerosis, and/or revascularization procedure), diabetes mellitus, hypertension, hypercholesterolemia, hyperlipidemia, deep venous thrombosis, pulmonary embolism, and other coagulopathy (eg, protein S or protein C deficiency or anticardiolipin antibody), physical inactivity, obesity, and smoking. Family medical history will be collected and should include history of coronary artery disease and early death from MI or cerebrovascular accident in first-degree relatives. Demographic information consists of the patient's age, sex, and race (as allowed by local law and regulations).
4. Both the initial leukemia diagnosis and the current screening diagnosis must be recorded.
5. Height and weight only at screening.
6. A complete physical examination must be performed at screening, on Cycle 1 Day1 prior to the first administration of study drug, and at the End-of-Treatment Visit. Physical examinations at other time points may be directed to relevant findings in the patient. ECOG status must be assessed during all physical examinations. Comprehensive eye exams should be performed at baseline (or at the next visit if not done at baseline for ongoing patients) and as clinically indicated.
7. Thyroid function test will measure the levels of TSH, free T3 and free T4. The test will be performed at screening and Day 1 of Cycle 3.
8. If a patient is ineligible based on a non-fasting triglyceride level, the test may be repeated with a fasting level to determine eligibility. Fasting serum triglycerides, specifically LDL cholesterol levels should be collected at baseline (or at the next visit if not done at baseline for ongoing patients) and then as clinically indicated.
9. An ECHO should be performed at the end of Cycle 3 only if clinically indicated and at the End-of-Treatment or Follow-up Visit only if abnormality develops during study.
10. The BM aspirate, with or without an optional biopsy, must occur **within 42 days** prior to the first dose of ponatinib and ± 7 days of the subsequent scheduled assessments. A BM aspirate is required every 3 months for CP patients, and at the end of Cycle 1, Cycle 2, and then every 2 months for AP, BP, and Ph+ ALL patients. A BM aspirate is performed at the End-of-Treatment Visit if it has been ≥ 12 weeks for CP and ≥ 8 weeks for AP or BP or Ph+ ALL since the last BM aspirate. Bone marrow aspirates and biopsies may be performed at other times when clinically indicated.
11. Samples of peripheral blood (all patients) and BM (BP and Ph+ ALL patients only)
12. Additional disease evaluations as appropriate to fully assess disease status in patients with extramedullary involvement; the site(s) of involvement must be assessed at screening and in subsequent disease evaluation points with appropriate laboratory tests or procedures.
13. PK blood sampling will be conducted as follows:

- Blood samples for PK analysis will be collected during both Cycle 1 and Cycle 2, immediately prior to the first dose (time 0), and 0.5, 1, 2, 4, 6, 8, and 24 hours after the first dose. The 24-hour sample will be collected prior to dosing on Day 2 for both cycles. Blood samples will also be collected prior to dosing on Cycle 1 Days 8, 15, and 22. An additional sample will be collected for AP, BP, and Ph+ ALL patients prior to dosing on Cycle 1 Day 28.
- Regarding Phase II portion patients, PK samples will not be collected.
- PK sample collection for patients who will be given 15 mg ponatinib daily in order to investigate PK linearity in Japanese patients, sampling time will be 0 (just before administration), 0.5, 1, 2, 4, 6, 8, and 24 hours after intake on Day 1 and Day 8 in Cycle 1, respectively.

14. Patients in phase I portion: informed consent should be obtained before the dosing on Day 1 of Cycle 2.

15. Fasting glucose levels should be collected at baseline (or at the next visit if not done at baseline for ongoing patients) and then as clinically indicated.

Unless otherwise specified, the manner in which Cycle 1 tests are performed should be repeated in later cycles. Screening tests must be performed within 21 days prior to the first dose of study drug (see exceptions for screening BM and pregnancy test, below). Otherwise, samples or activities should occur **within 3 days** of the scheduled study day unless otherwise noted in the Schedule of Events. Bone marrow aspirates should occur **within 7 days** of the scheduled study day.

Day 28 procedure/laboratory tests of a finishing cycle may be performed on Day 1 of the next cycle, unless otherwise specified.

Procedures for determining response criteria in CP, and AP, BP, and Ph+ ALL patients are summarized below. These procedures are also listed in following sections by study phase.

Chronic Phase:

- Complete hematologic response (CHR): Hematologic response determination occurs for CP patients with each CBC and differential. The criteria for CHR also include the absence of extramedullary involvement, so an assessment of hepatosplenomegaly must be recorded at each physical examination.
- Major cytogenetic response (MCyR): For CP patients, BM aspirate for morphology and cytogenetics occurs every 3 months. Conventional banding for cytogenetics is required. More frequent aspirates are allowed, but these are not required.
- Major molecular response (MMR): Collection of peripheral blood for determination of molecular response occurs every 3 months, according to the same schedule as the BM aspirates.

Accelerated Phase, BP, and Ph+ ALL:

- Major hematologic response (MaHR): For AP, BP, and Ph+ ALL patients, hematologic response determination requires an assessment of extramedullary involvement by physical examination, a CBC and differential, and a BM aspirate. An assessment of hepatosplenomegaly must be recorded at each physical examination. A BM aspirate is required on Cycle 1 Day 28, Cycle 2 Day 28, and at the end of each even-numbered cycle thereafter.
- Major cytogenetic response (MCyR): For AP, BP, and Ph+ ALL patients, BM aspirate for morphology and cytogenetics occurs on Cycle 1 Day 28, Cycle 2 Day 28, and then every 2 months. Conventional banding for cytogenetics is required. More frequent assessments are allowed but are not required.
- Major molecular response (MMR): Collection of peripheral blood for determination of molecular response occurs every 2 months, according to the same schedule as the BM aspirates. For BP and Ph+ ALL, a sample of marrow aspirate for molecular response is also collected.

7.1 Screening Period Procedures, Medical History, and Demographics

All screening tests must be performed within 21 days prior to the first dose of ponatinib with the exception of the screening BM aspirate (within 42 days) and screening pregnancy test (within

7 days). Patients must continue to maintain laboratory values within eligibility parameters if any given procedure or laboratory test is repeated prior to the start of ponatinib on Cycle 1 Day 1.

- Informed Consent
  - Informed Consent must be documented by a signed consent form prior to any screening activities not otherwise part of the patient's care.
- Medical and surgical history and demographics
  - Medical and surgical history includes diagnoses, therapies, medical and surgical treatments, and current medications, and must include any history of ischemic heart disease (including angina, MI, acute coronary syndrome, and/or coronary revascularization procedures), valvular heart disease, CHF, arrhythmias, myocarditis, peripheral arterial occlusive disease (including claudication, distal extremity amputation, angioplasty, and/or revascularization procedure), stroke (including TIA, cerebrovascular atherosclerosis, and/or revascularization procedure), diabetes mellitus, hypertension, hypercholesterolemia, hyperlipidemia, deep venous thrombosis, pulmonary embolism, any other coagulopathy (eg, protein S or protein C deficiency or anticardiolipin antibody), physical inactivity, obesity, and smoking. Family medical history will be collected and should include history of coronary artery disease and early death from MI or cerebrovascular accident in first-degree relatives.
  - Demographic information consists of the patient's age, gender, and race.
- Cancer diagnosis and prior cancer therapy
  - The initial leukemia diagnosis, including date and the current diagnosis at the time of screening, and the date of onset of the current diagnosis, need to be recorded. Prior therapy history consists of the specific oncologic regimens a patient has received, the dates of the regimen and the best response to the regimen, and the reason for failure of or intolerance to each regimen. Stem cell transplant or experimental therapy history is also recorded.
- Current and past BCR-ABL mutation history
  - Any previously identified mutations, and the dates of identification, must be recorded.
- Vital signs, including height and weight
- Physical examination including hepatosplenomegaly, comprehensive eye exam, and ECOG performance status. If the comprehensive eye exam was not performed at baseline, it should be done at the next visit for ongoing patients.
- CBC with differential
- Serum chemistry, including amylase and lipase
- Serum triglycerides
- PT and PTT
- Pregnancy test (if applicable)
- 12-lead ECG

- ECHO
- AEs and concomitant medications and/or concurrent treatment
- BM aspirate and cytogenetic response
  - The BM aspirate, with or without biopsy, must occur within 42 days prior to the first dose of ponatinib and ± 7 days of all other scheduled assessments
- Molecular response
  - Samples of peripheral blood (all patients) and BM (BP and Ph+ ALL patients only)
- Additional disease assessments (eg, evaluation of extramedullary disease sites in AP, BP, and Ph+ ALL)
- CCI
- CCI

7.1.1 Screen Failures

Patients who have signed informed consent and subsequently fail to meet the inclusion and/or exclusion criteria are defined as screen failures. For all screen failures, the investigator is to maintain a screening log that documents the patient initials and reason(s) for screen failure. A copy of the log should be retained in the investigator's study files.

7.2 Treatment Period Procedures

An eCRF must be completed for any patient who receives study drug.

Patients will be instructed to take the prescribed number of tablets with water, with or without food, at approximately the same time each day.

Procedures to be performed during the study are listed in Table 5 for CP patients and Table 6 for AP, BP, and Ph+ ALL patients.

The following should be noted with regard to the primary and secondary endpoints:

Chronic Phase

- CHR determination occurs with each CBC and differential.
- For MCyR, BM aspirate for morphology and cytogenetics is required every 3 months.
- For MMR, peripheral blood collection is required every 3 months.

Accelerated Phase, BP, and Ph+ ALL

- MaHR determination occurs with each physical examination, CBC and differential, and BM aspirate.
- For MCyR, BM aspirate for morphology and cytogenetics is required on Day 28 of Cycles 1, 2, and then every 2 months.
- For MMR, peripheral blood collection is required every 2 months.

For all patients, an assessment of hepatosplenomegaly must be recorded at each physical examination.

7.3 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. An End-of-Treatment reason must be recorded for any patient who receives study drug and/or is enrolled in the study.

The following tests and procedures are required at the End-of-Treatment (or early termination) Visit for all patients:

- Vital signs
- Complete physical examination, including hepatosplenomegaly and ECOG performance status
- CBC with differential
- Serum chemistry including amylase and lipase
- Pregnancy test, if applicable
- 12-lead ECG
- ECHO
- AEs and concomitant medications and/or concurrent treatment
- BM aspirate and cytogenetic response
- Molecular response
  - Samples of peripheral blood (all patients) and BM (BP and Ph+ ALL patients only)
- BCR-ABL Mutation detection
- Molecular genetics

7.4 Follow-up

The Follow-up Visit will be conducted 30 days (± 7 days) after the last dose of study drug.

The following tests and procedures are required at the Follow-up Visit for all patients:

- Vital signs
- Complete physical examination, including hepatosplenomegaly and ECOG performance status
- CBC with differential
- Serum chemistry, including amylase and lipase
- ECHO
- AEs and concomitant medications and/or concurrent treatment

7.5 Survival Follow-up

Survival data for all patients will be collected every 12 weeks ± 2 weeks starting after the last dose of study drug for up to 60 months from initiation of therapy. These data do not need to be obtained during a visit, and phone contact is acceptable.

8 ADVERSE EVENT REPORTING

8.1 Adverse Events

8.1.1 Adverse Event Definition

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, and that does not necessarily have to have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Any worsening of a pre-existing condition that is temporally associated with the use of the study drug (eg, occurs after the first dose of study drug) is also an AE.

Adverse events include:

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

8.1.2 Abnormal Test Findings

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

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

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

8.1.3 Performing Adverse Event Assessments

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

For all AEs, the investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious AE (SAE; see Section 8.2) requiring immediate notification to CCI).

8.1.4 Reporting Period

Serious AEs require immediate notification to CCI beginning from the time the patient provides informed consent, which is obtained prior to the patient's participation in the clinical study (ie, prior to undergoing any study-related procedure and/or receiving investigational product), through and including 30 days after the last administration of investigational product. Any SAE occurring any time after the reporting period must be promptly reported to ARIAD Pharmacovigilance and Risk Management or its designated representative (within 24 hours of the investigator's awareness) if a causal relationship to the investigational product is suspected.

For all enrolled patients, AEs (serious and non-serious) should be recorded on the eCRF during the on-study period, which begins with signing the informed consent form and concludes 30 days following the last dose of study drug.

8.1.5 Adverse Event Severity

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

- *Mild (Grade 1):* The AE is noticeable to the patient but does not interfere with routine activity. The AE does not require discontinuing administration or reducing the dose of the study drug.
- *Moderate (Grade 2):* The AE interferes with routine activity but responds to symptomatic therapy or rest. The AE may require reducing the dose, but not discontinuing administration of the study drug.
- *Severe (Grade 3):* The AE significantly limits the patient's ability to perform routine activities despite symptomatic therapy. In addition, the AE leads to discontinuing administration or reducing the dose of the study drug.
- *Life-Threatening (Grade 4):* The AE requires discontinuing administration of the study drug. The patient is at immediate risk of death.
- *Death (Grade 5):* The patient dies as a result of AE(s).

8.1.6 Causality

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

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

The investigator will use medical consideration and the following categories of causality to determine the relatedness of an AE with study drug, based on the following definitions. Not all criteria in each category of relatedness must be present. Also, if an AE related to study drug continues after the follow-up visit, the patient must be followed until the event returns to baseline (or becomes less than CTCAE grade 1), or the investigator judges that it becomes stable, chronic, or irreversible.

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

Possibly Related (drug related)

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

Probably Related (drug related)

- There is evidence of exposure to study drug
- The temporal sequence of the AE onset relative to administration of 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
- 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

8.1.7 Expectedness

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

8.2 Serious Adverse Events and Adverse Events of Special Interest

8.2.1 Serious Adverse Event Definition

The investigator or the sponsor may determine the seriousness of an AE based on the following. An AE is considered an SAE if at least one of the following conditions applies:

- *Death:* An AE that results in death is any patient death within 30 days of the last dose of study drug administration. The cause of death or AE that resulted in a fatal outcome is the SAE.
- *Life-threatening AE:* An AE that places the patient, in the view of the investigator or the sponsor, at immediate risk of death from the event as it occurred (ie, this does not include an event that, had it occurred in a more severe form might have caused death).
- *Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions* is defined as any substantial disruption of a person's ability to conduct normal life functions.
- *Inpatient hospitalization or prolongation of existing hospitalization:* Hospitalization refers to admission of a patient into a hospital for any length of time.
- *A congenital anomaly/birth defect:* A fixed, permanent impairment established at or before birth
- *Cancer:* Occurrence or diagnosis of a new cancer during the study is considered an SAE.
- Any AE associated with an overdose of study drug. An overdose of study drug is defined as an occurrence of administered dose exceeding that which is prescribed by the investigator per protocol.

- *Important medical event:* Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not result in death, be life-threatening, or require hospitalization. However, if it is determined that the event may jeopardize the patient and/or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical 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.
- 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.
- Hospitalizations: Adverse events that are reported from clinical studies and require hospitalization or prolongation of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a health care facility meets these criteria. Adverse events that require emergency room care that do not result in hospital admission are not SAEs unless assessed by the investigator to be an important medical event. Hospitalization does not include the following:
    - Hospice facilities
    - Respite care
    - Skilled nursing facilities
    - Nursing homes
    - Routine emergency room admissions
    - Same day surgeries (as outpatient/same day/ambulatory procedure)

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

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

Hospitalization or prolongation of hospitalization for scheduled therapy of the target malignancy of the study is not considered an SAE

8.2.2 Identification of Adverse Events of Special Interest

The following terms have been identified as adverse events of special interest (AESIs) for ponatinib. These events generally meet one of the seriousness criteria and should therefore be handled as SAEs. However, in the event that an AESI is not fatal or life-threatening, or does not require or prolong hospitalization, it should be classified as medically important and, therefore, serious. All AESIs are to be classified as SAEs.

- **Myocardial infarction**: the Third Universal Definition of Myocardial Infarction (Thygesen et al, 2012) is used to define MI. Acute MI is used in a clinical setting when there is evidence of myocardial necrosis consistent with myocardial ischemia. Any one of the following constitutes MI:
  - 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 1 of the following:
    - Symptoms of ischemia
    - New or presumed new significant ST-segment T-wave changes or new left branch bundle 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 by angiography or autopsy of an intracoronary thrombus
  - Cardiac death, with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB; death occurred before cardiac biomarkers were obtained or would be increased
  - Percutaneous coronary intervention-related MI, arbitrarily defined by elevation of cTn values (greater than 5 x 99th percentile URL) in patients with normal baseline values (less than 99th percentile URL), or a rise of cTn values greater than 20% if baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, (ii) new ischemic changes, (iii) angiographic

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

- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in a 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, arbitrarily defined by elevation of cardiac biomarker values (greater than 10 x 99th percentile URL) in patients with normal baseline cTN values (less than 99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, (ii) angiographic-documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

- **Prior MI** is defined by any one of the following criteria:
  - Pathological Q waves with or without symptoms in the absence of non-ischemic causes
  - Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause
  - Pathological findings of a prior MI
- **Angina**: symptoms of myocardial ischemia without diagnostic evidence of an MI by cardiac biomarkers, ECG, imaging studies, or coronary angiography
- **Coronary artery disease**: an event in which coronary athero- or arteriosclerosis is reported on angiogram (without evidence of thrombus), and no associated angina or evidence of an MI are reported (Thygesen et al, 2012)
- **Stroke**: (ischemic or hemorrhagic) evidence of infarction or hemorrhage of CNS tissue, based either on neuroimaging (preferably including diffusion-weighted magnetic resonance imaging [MRI]) or clinical signs of permanent neurologic dysfunction (Easton et al, 2009)
- **Transient ischemic attack (TIA)**: transient episode of neurodysfunction caused by focal brain, spinal cord, or retinal ischemia, without evidence of acute infarction on neuroimaging (preferably including diffusion-weighted MRI) (Easton et al, 2009)
- **Peripheral arterial occlusive disease**: evidence of athero- or arteriosclerosis (with or without thrombus) on angiography.

8.2.3 Reporting Serious Adverse Events and Adverse Events of Special Interest

The Investigator or designee must notify CCI the ICCC for the study, within 24 hours after becoming aware of an SAE or AESI. Additional or follow-up information on an SAE or AESI must also be reported immediately. This timeframe also applies to additional new information (follow-up) on previously forwarded SAEs or AESIs. Should the FDA or National Regulatory Authorities require that the sponsor submit additional data on the event, the Investigator will be asked to provide those data to the sponsor in a timely fashion.

8.2.4 Information to be Provided by the Investigator for a Serious Adverse Event or Adverse Event of Special Interest

Information should be provided on the Serious Adverse Event Report form signed and dated by the investigator. The sponsor or designee will require all of the following information about the patient and the event:

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

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

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

8.2.5 Follow-up Information on a Serious Adverse Event or Adverse Event of Special Interest

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 (including AESIs), the investigator is obligated to pursue and provide information to CCI In addition, an Investigator may be requested by CCI to obtain specific information in an expedited manner. This information may be more detailed than that captured on the AE form. In general, this will include a description of the SAE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes, such as concomitant medication and illnesses, must be provided.

Required Follow-up for Serious Adverse Events or Adverse Events of Special Interest

There should be routine follow-up for 30 days after study drug discontinuation or study withdrawal in all patients in order to monitor for the occurrence of SAEs/AESIs. If an SAE/AESI continues after the follow-up visit, the patient must be followed until the event returns to baseline (or becomes less than CTCAE grade 1), or the investigator judges that it becomes stable, chronic, or irreversible. The medical monitor may specify a longer period of time if required to assure the safety of the patient.

Sponsor Responsibility for Expedited Safety Reports

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

The investigator and Institutional Review Board (IRB) will determine if the informed consent requires revision. The investigator should also comply with IRB/EC procedures for reporting any other safety information.

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

8.3 Other Safety Issues

8.3.1 Pregnancy

Ponatinib does not induce microbial or mammalian cell gene mutations in vitro and does not produce chromosomal aberrations in vitro or in vivo. Nothing is known about the effects of ponatinib on reproductive function.

Females and males who are fertile will be informed as to the potential risk of conception while participating in this study, and will be advised that they must use effective contraception from enrollment through at least 4 months after the end of treatment. A pregnancy test will be performed on each pre-menopausal female of childbearing potential immediately prior to the first dose of study drug, and again at treatment discontinuation. A negative pregnancy test must be documented prior to administration of study drug.

Patients need to be in complete abstinence from sexual intercourse 4 weeks before the initial drug dosing or need to use at least one of the contraceptive methods suggested below. Other contraceptive options are to be discussed with the investigator, who should advise the patient how to use them properly.

- Hormonal contraception
- Intrauterine device
- Spermicide
- Barrier method of contraception

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

The investigator must immediately (within 24 hours of the investigator's awareness) report follow-up information to the sponsor regarding the course of the pregnancy, including perinatal and neonatal outcome, regardless of whether the patient has discontinued participation in the study.

8.3.2 Overdose

In the event of an overdose, the sponsor should be contacted to discuss details of the overdose and formulate a clinical management plan. No information regarding overdose of ponatinib in humans is available. No specific antidotes exist for the treatment of ponatinib overdose. In the

event of an accidental overdose, the patient should be monitored for possible signs of toxicity and general supportive care should be provided.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

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

Data from patients in the phase II expansion phase will be summarized together with data from patients in the dose-escalation cohorts, as appropriate within disease group, with each disease type summarized separately (CP-CML, AP-CML, BP-CML, Ph+ALL), and with the advanced phases (AP-CML, BP-CML, and Ph+ALL) pooled. Descriptive statistics (such as means, medians, standard deviations, ranges for continuous data, and percentages for categorical data) will be used to summarize patient characteristics, treatment administration/compliance, efficacy, safety, and PK parameters. Data will also be displayed graphically, where appropriate.

A clinical study report will be written once primary endpoint data are available for all patients (approximately 6 months after the last patient is enrolled), which will be the basis of a regulatory submission. Further follow-up data will be summarized separately.

9.2 Analysis Populations

DLT Evaluable Population (phase I only): This population includes all patients who complete at least 75% of their planned doses during Cycle 1, unless missed doses are due to AEs.

Treated Population: This population includes all patients who have received at least 1 dose of study drug.

9.3 Study Endpoints

9.3.1 Primary Endpoints

Phase I

Safety of the recommended dose of oral ponatinib in Japanese patients with CML who are resistant or intolerant to dasatinib or nilotinib, or with Ph+ ALL who are resistant or intolerant to prior TKIs

Phase II

In the phase II component, the primary efficacy endpoints will be:

- For CML patients in CP at study entry: MCyR, defined as CCyR or PCyR
  - CP patients in CCyR are not eligible for this study.
- For CML patients in AP, BP, or Ph+ ALL at study entry: MaHR, defined as CHR or no evidence of leukemia (NEL)
  - AP, BP, and Ph+ ALL patients in MaHR are not eligible for this study.

9.3.2 Secondary Endpoints

Secondary efficacy endpoints will be:

- For CML patients in CP:
  - Hematologic responses: CHR
  - Cytogenetic responses: confirmed MCyR
  - Molecular responses: MMR
- For CML patients in AP or BP or Ph+ ALL patients:
  - Cytogenetic responses: CCyR, PCyR, confirmed MCyR
  - Molecular responses: MMR
- For all patients: time to response (TTR), duration of response, progression-free survival (PFS), and OS

9.3.3 Exploratory Endpoints

Exploratory endpoints for all patients:

CCI [redacted]

9.4 Determination of Sample Size

Six patients will be enrolled at each ponatinib dose level of 30 mg and 45 mg to allow for adequate assessment of tolerability and evidence of clinical activity. The number of patients at each dose level is consistent with phase I dose-finding studies.

An additional 3 patients will be included at 15 mg for the purposes of PK sample collection during Cycle 1 in order to determine PK linearity in Japanese patients. These patients will be allowed to dose-escalate to the recommended dose (at the discretion of the investigator) and will be assessed for efficacy and safety as phase II patients.

The patients who participated in phase I component will also be assessed for efficacy and safety together with patients enrolled in phase II component.

For phase II component, the needed patient number is calculated as follows:

In preliminary data from the PACE phase II study of ponatinib in patients with CML or Ph+ ALL who were resistant or intolerant to nilotinib or dasatinib or who have a T315I mutation, MCyR rate was 47% (116/248) in CP-CML, MaHR rate was 67% (37/55) in AP-CML and 37% (33/89) in BP-CML and Ph+ALL, respectively. Based on this result, it is assumed 40% MCyR rate for CP-CML and 40% MaHR rate for AP-CML, BP-CML, and Ph+ALL.

Because effective therapy has not yet been established for these patients, it is anticipated that more than 10 % MCyR rate for CP-CML and more than 10% MaHR rate for AP-CML, BP-CML, and Ph+ALL is considered clinically relevant.

It is assumed 40 % efficacy rate and 10% uninteresting rate for MCyR rate as well as MaHR rate for AP-CML, BP-CML, and Ph+ALL. Because the target population is very small, a 1-sided 5%

significance level is used for this sample-size calculation. Sixteen patients in each group (CP-CML,AP-CML, BP-CML, and Ph＋ALL) are needed to retain 80% power for a testing using binomial distribution. Assuming 1 ineligible patient per group would be included, 17 patients per group (total 34 patients) are planned to be enrolled.

Because analysis of the primary endpoint is based on combined data from the phase I and phase II components, total patient enrollment in either phase should be sufficient to meet these target patient totals.

In addition, for these disease groups (and possibly other subgroups of interest) confidence intervals (CIs) will be calculated; in the event these contain estimates from the global pivotal phase II ponatinib PACE study (AP24534-10-201), a Bayesian analysis will be performed, using data from the PACE study as the prior distribution (more details to be provided in the Statistical Analysis Plan). This will allow for more precise probabilistic statements about the combined study population in each disease group, and will also provide a method of inference if fewer than 5 patients are enrolled in any of the groups.

9.5 Efficacy Analysis

All efficacy analyses will be performed separately by disease group: CP vs. AP vs. BP vs. Ph+ ALL, and will include all patients in the treated population. Additionally, an analysis of the primary efficacy endpoint will be performed, pooling the AP, BP, and Ph+ALL populations.

The primary analysis will be performed after the last patient enrolled has completed six 28-day cycles of treatment, and will include all data collected at that time.

9.5.1 Definitions of Efficacy Endpoints

Primary efficacy endpoints for this study are defined as follows:

- CP-CML: Major cytogenetic response, which is defined as CCyR or PCyR. Patients entering the study already in PCyR must achieve a CCyR in order to be considered as achieving an MCyR. The criteria for response are given in Appendix A.
- AP-CML, BP-CML, Ph+ ALL: Major hematologic response, which is defined as CHR and NEL. Major hematologic response will be confirmed by a peripheral blood complete blood count (CBC) and differential no earlier than 28 days after the response is observed. The criteria for response are given in Appendix A.

Secondary efficacy endpoints for this study are defined as follows:

- Confirmed MCyR, which is defined as 2 assessments of CCyR or PCyR at least 28 days apart. For CP patients entering the study in PCyR, confirmed MCyR will be defined as 2 assessments of CCyR at least 28 days apart.
- Major molecular response (as defined in Appendix A)
- Duration of response, which is defined as the interval between the first assessment at which the criteria for response are met, until the criteria for progression (as defined in Appendix A) are met, censored at the last date at which the criteria for response are met

- Progression-free survival, which is defined as the interval from the first dose of study treatment until the criteria for progression (as defined Appendix A) or death are met, censored at the last response assessment
- Overall survival, which is defined as the interval from the first dose of study treatment until death, censored at the last date at which patient was known to be alive
- Time to response, which is defined as the interval from the first dose of study treatment until the criteria for response are first met, censored at the last assessment of response

Exploratory endpoints for this study are defined as follows:

- CCI
- [redacted]

9.5.2 Primary Efficacy Endpoint Analysis

CP-CML Patients

The primary analysis of the primary efficacy endpoint of MCyR will be performed using a 1-sided exact 95% CI for the MCyR rate and will be based on the total CP-CML patients enrolled in the dose-escalation phase (including an additional 3 patients dosed at 15 mg) and expansion phase. Major cytogenetic response rate is defined as the proportion of patients who have achieved a CCyR or PCyR after initiation of study treatment. Patients entering the study already in PCyR must achieve a CCyR in order to be considered a success for the MCyR rate.

AP-CML, BP-CML, Ph+ ALL Patients

Major hematologic response rate is defined as the proportion of patients who have achieved a confirmed CHR or NEL after initiation of study treatment. The primary analysis of the primary efficacy endpoint of MaHR will be performed using a 1-sided exact 95% CI for MaHR rate and will be based on the total patients enrolled in the dose escalation phase (including an additional 3 patients dosed at 15 mg) and expansion phase for combined data across these disease group (AP-CML and BP-CML/Ph+ ALL).

9.5.2.1 Data Handling Rules for the Primary Analyses of the Primary Efficacy Endpoint

The key data handling rules for the primary efficacy analyses are as follows:

- At any given cytogenetic assessment, if fewer than 20 metaphases are examined, that assessment will be treated as missing for the determination of MCyR.
- A BM aspirate is required for a patient to be considered as meeting the criteria for MaHR.
- For a given visit, if all of the data required to support an assessment of response (see Appendix A) are not available, the patient will be considered as not a success for that particular visit.

9.5.2.2 Secondary Endpoint Analyses

- Confirmed MCyR: the confirmed MCyR rate is defined as the proportion of patients who have achieved a confirmed CCyR or PCyR after the initiation of study treatment. Patients entering the study already in PCyR must achieve a confirmed CCyR in order to be considered a success for the confirmed MCyR rate. The analysis will be performed using a 1-sided exact 95% CI for the confirmed MCyR rate.
- Duration of response will be estimated using the Kaplan-Meier method. The median duration of response and a 1-sided exact 95% CI will be calculated.
- Progression-free survival, OS, and TTR will be estimated using the Kaplan-Meier method. The median duration of each endpoint and a 1-sided exact 95% CI will be calculated.

9.6 Safety Analysis

All patients receiving at least 1 dose of study drug will be considered evaluable for safety. AE incidence rates as well as the frequency of occurrence of overall toxicity, categorized by toxicity grades (severity), will be described for each cohort of the study. Similar analyses will be performed on AESIs. Listings of laboratory test results and any imaging studies (including ECGs) will also be generated, and descriptive statistics summarizing changes in these assessments over time will be presented.

9.7 Interim Analysis

No interim analysis is planned for this study.

9.8 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 treatment group in the clinical study report.

10 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, sponsor personnel or designee and the investigator will review the protocol, Clinical Investigator's Brochure, eCRFs and instructions for their completion, procedure for obtaining informed consent, and procedure for reporting AEs. A qualified representative of the sponsor monitors the conduct of the study by visiting the site and by contacting the site by telephone. During the visits, information recorded in the eCRFs is verified against source documents. The sponsor's medical monitor reviews the data for safety information. The sponsor's clinical data associates or designees review the data for legibility, completeness, and logical consistency. Additionally, the sponsor's clinical data associates 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 are 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 eCRF against source documents.

10.1 Investigators and Study Administrative Structure

A list of investigators and study administrative structure are shown in separate pamphlets.

10.2 Study Monitoring

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

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

11 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.

11.1 Institutional Review Board Approval

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

11.2 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 site's proposed informed consent document should be submitted to the sponsor for review and comment before submission to the site's 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 these 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.

11.3 Patient Confidentiality

All unpublished information that the sponsor gives to the investigator shall be kept confidential and shall not be published or disclosed to a third party without the prior written consent of the sponsor.

12 DATA HANDLING AND RECORD KEEPING

12.1 Case Report Forms and Study Records

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

12.2 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 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 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.*

12.3 Retention of Data

Trial documents must be retained according to JGCP Items 26 and 41.

- The sponsor must maintain trial documents until a longer period of the following dates: a day of approval for manufacture and sales, 3 years after trial discontinuation, or 3 years after the study completion. The trial documents include protocol, contracts, clinical study reports, eCRFs, monitoring reports, audit reports, and trial data as well as study drug inventory records with information regarding manufacture date, manufacture procedures, manufactured amount, quality of safety, distribution to the site(s), return, and destruction of the study drug. If re-inspection for the study drug is required after approval for manufacture and sales, the

documents that contain the information about efficacy and safety of the drug must be collected and maintained for a longer period of the following points: 5 years after approval or the completion date of the re-inspection.

- The head of the site must maintain trial documents until a longer period of the following dates: a day of approval for manufacture and sales, 3 years after trial discontinuation, or 3 years after the study completion. The trial documents include protocol, contracts, clinical study reports, eCRFs, monitoring reports, audit reports, and trial data as well as study drug inventory records with the information regarding manufacture date, manufacture procedures, manufactured amount, quality of safety, distribution to the site(s), return, and destruction of the study drug. Trial documents should be retained for a longer period if required by applicable regulatory requirements or by agreement with the sponsor. Thereafter, records will not be destroyed without giving the sponsor prior written notice and the opportunity to further store such records, at the sponsor's cost and expense.

12.4 Termination of Study

The sponsor may terminate the study at any time for any of the following reasons:

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

13 PUBLICATION AND DISCLOSURE POLICY

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

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

14 REFERENCES

Apperley JF, Cortes JE, Kim D-W, et al. Desatinib in the treatment of Chronic Myeloid Leukemia in Accelerated Phase After Imatinib Failure: The START Trial. Clin Oncol. 2009;27:3472-3479.

Baccarani M, Cortes J, Pane F, Niederwieser D, Saglio G, Apperley J, Cervantes F, Deininger M, Gratwohl A, Guilhot F, Hochhaus A, Horowitz M, Hughes T, Kantarjian H, Larson R, Radich J, Simonsson B, Silver RT, Goldman J, Hehlmann R; European LeukemiaNet. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. J Clin Oncol. 2009;27(35):6041-6051.

Branford S, Rudzki Z, Walsh S, et al. Detection of BCR-ABL mutations in patients with CML treated with imatinib is virtually always accompanied by clinical resistance, and mutations in the ATP phosphate-binding loop (P-loop) are associated with a poor prognosis [published online ahead of print March 6, 2003]. Blood. 2003;102(1):276-283. doi:10.1182/blood-2002-09-2896.

Cortes J, Hochhaus A, Hughes T, Kantarjian H. Front-line and salvage therapies with tyrosine kinase inhibitors and other treatments in chronic myeloid leukemia [published online ahead of print January 10, 2011]. J Clin Oncol. 2011;29(5):524-531. doi:10.1200/JCO.2010.31.3619.

Deininger MWN, Goldman J, Melo J. The Molecular Biology of Chronic Myeloid Leukemia. Blood. 2000;96:3343-3356.

Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Council. Stroke. 2009; 40:2276-2293.

Jabbour E, Kantarjian H, Jones D, et al. Frequency and clinical significance of BCR-ABL mutations in patients with chronic myeloid leukemia treated with imatinib mesylate [published online ahead of print July 20, 2006]. Leukemia. 2006;20(10):1767-1773. doi:10.1038/sj.leu.2404318.

Jones D, Kamel-Reid S, Bahler D, et al. Laboratory practice guidelines for detecting and reporting BCR-ABL drug resistance mutations in chronic myelogenous leukemia and acute lymphoblastic leukemia: a report of the Association for Molecular Pathology. J Mol Diagn. 2009;11(1):4-11. doi:10.2353/jmoldx.2009.080095.

Kantarjian H, Giles F, Wunderle L, et al. Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. N Engl J Med. 2006;354:2542-2551.

Kantarjian H, O'Brien S, Talpaz M, et al. Outcome of patients with Philadelphia chromosome-positive chronic myelogenous leukemia post-imatinib mesylate failure. Cancer. 2007;109:1556-1560.

Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2010; 362(24):2260-2270.

O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, Cornelissen JJ, Fischer T, Hochhaus A, Hughes T, Lechner K, Nielsen JL, Rousselot P, Reiffers J, Saglio G, Shepherd J, Simonsson B, Gratwohl A, Goldman JM, Kantarjian H, Taylor K, Verhoef G, Bolton AE, Capdeville R, Druker BJ; IRIS Investigators. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2003;348(11):994-1004.

O'Hare T, Eide CA, Deininger MWM. BCR-ABL kinase domain mutations, drug resistance and the road to ac of chronic myeloid leukemia. Blood. 2007;110:2242-2249.

O'Hare T, Deininger MWN, Eide CA, et al. Targeting the BCR-ABL signaling pathway in therapy-resistant Philadelphia chromosome-positive leukemia [published online ahead of print November 22, 2010]. Clin Cancer Res. 2011;17(2):212-221. doi:10.1158/1078-0432.CCR-09-3314.

Pinilla-Ibarz J, Bello C. Modern approaches to treating chronic myelogenous leukemia. Curr Oncol Rep. 2008;10(5):365-371.

Talpaz M, Shah N, Kantarjian H, et al. Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. N Engl J Med. 2006;354:2531-2541.

Terasawa T, Dahabreh I, Trikalinos TA. BCR-ABL mutation testing to predict response to tyrosine kinase inhibitors in patients with chronic myeloid leukemia. Version 2. PLoSCurr. 2010 December 15 [revised 2011 January 28].

Thygesen K, Alpert JS, Jaffe AS. Third Universal Definition of Myocardial Infarction. Circulation. 2012;126:2020-2035.

15 APPENDICES

APPENDIX A Response Criteria

Baseline information appropriate to the patient's specific diagnosis should be collected prior to the first dose of ponatinib. The information may be collected as part of this study or from the patient's medical record as long as it is within the time span specified in the Schedule of Events in Section 7 (Table 5 and Table 6) of this protocol.

RESPONSE CRITERIA FOR CHRONIC MYELOGENOUS LEUKEMIA (CML) AND PHILADELPHIA CHROMOSOME POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA (Ph+ ALL)

Note: These criteria are adapted from Talpaz et al, 2006, O'Brien et al, 2003, and Kantarjian et al, 2010.

Hematologic Response

1. Chronic Phase (CP) Chronic Myelogenous Leukemia(CML)
   a. Complete Hematologic Response (CHR)
      i. White blood cells (WBC) ≤institutional upper limit of normal
      ii. Platelets <450,000/mm^3
      iii. No blasts or promyelocytes in peripheral blood
      iv. <5% myelocytes plus metamyelocytes in peripheral blood
      v. Basophils in peripheral blood <5%
      vi. No extramedullary involvement (including no hepatomegaly or splenomegaly)
2. Accelerated Phase (AP) and Blast Phase (BP) CML and Ph+ ALL
   a. Major Hematologic Response (MaHR)
      vii. Complete Hematologic Response (CHR)
         a) WBC ≤ institutional upper limit of normal
         b) Absolute neutrophil count (ANC) ≥ 1000/mm^3
         c) Platelets ≥ 100,000/ mm^3
         d) No blasts or promyelocytes in peripheral blood
         e) Bone marrow (BM) blasts ≤ 5%
         f) < 5% myelocytes plus metamyelocytes in peripheral blood
         g) Basophils in peripheral blood < 5%
         h) No extramedullary involvement (including no hepatomegaly or splenomegaly)

viii. No evidence of Leukemia (NEL)

a) WBC ≤institutional upper limit of normal

b) No blasts or promyelocytes in peripheral blood

c) BM blasts ≤ 5%

d) < 5% myelocytes plus metamyelocytes in peripheral blood

e) Basophils in peripheral blood < 5%

f) No extramedullary involvement (including no hepatomegaly or splenomegaly)

g) At least 1 of the following: (i) 20,000/mm^3 ≤Platelets <100,000/mm^3; (ii) 500/mm^3 ≤ANC <1000/mm^3

Cytogenetic Response

The criteria for cytogenetic response are derived from Kantarjian et al, 2006, and Talpaz et al, 2006, as well as the National Comprehensive Cancer Network (NCCN) clinical practice guidelines (accessed February 2007).

At least 20 metaphase cells should be examined. If fewer metaphases are available, the absolute and percentage values should be reported. Peripheral blood cells may not be used.

Major Response (MCyR)	**Complete Response (CCyR)**	No Ph+ cells
	Partial Response (PCyR)	1%-35% Ph+ cells
Minor Response		36%-65% Ph+ cells
Minimal Response		66 %-95% Ph+ cells
No Response		96%-100% Ph+ cells

Major Molecular Response (Baccarani et al, 2009)

A major molecular response (MMR) is defined as a ratio of reverse transcribed transcript of BCR-ABL to ABL ≤0.1% on the international scale (equivalent to a 3-log reduction in transcript).

Progression Criteria

Progression from CP (O'Brien et al, 2003):

1. Death
2. Development of AP or BP
3. Loss of CHR (in the absence of cytogenetic response)

Confirmed by development in complete blood counts (CBCs) at least 4 weeks apart

4. Loss of MCyR
5. Increasing WBC in patient without CHR defined by:

Doubling of WBC to > 20K on two occasions at least 4 weeks apart (after the first 4 weeks of therapy)

Progression from AP (Apperley et al, 2009)

1. Death
2. Development of confirmed BP
3. Loss of previous major or minor hematologic response over a 2-week period
4. No decrease from baseline levels in percentage blasts in peripheral blood or BM on all assessments over a 4-week period

Progression from BP or Ph+ ALL (Talpaz et al, 2006)

1. Death
2. Increasing blasts in peripheral blood or BM over a 4 week period

APPENDIX B Prohibited Drugs Affecting the QT Interval

The list of drugs that can be associated with Torsades de Pointes or prolonged QT interval can be found online at

www.azcert.org/medical-pros/drug-lists/bycategory.cfm.

This online site does not include all prohibited medications and should be used as a guideline. Refer to the prescribing information to determine if a particular medication can be associated with Torsades de Pointes or prolonged QT interval.

Three categories of drugs are listed on this website. Concomitant use of drugs in the first category (Drugs with Risk of Torsades de Pointes) is prohibited. Agents in the two categories of lesser risk (Drugs with Possible Risk of Torsades de Pointes; and Drugs with Conditional Risk of Torsades de Pointes) should be avoided.

APPENDIX C Medications that are Strong Inhibitors or Inducers of CYP3A4/5/7

The list of drugs that are strong inhibitors or inducers of CYP3A4/5/7, and thereby concomitant administration with ponatinib could result in clinically relevant drug-drug interactions, can be found online at

http://medicine.iupui.edu/clinpharm/DDIs/ClinicalTable.aspx.

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm116617.htm

Drugs listed should be avoided if possible. This online site should be used as a guideline; refer to the prescribing information to determine if a particular medication is a strong CYP3A4/5/7 inhibitor or inducer.

APPENDIX D National Cancer Institute Common Terminology Criteria for Adverse Events

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

ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

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