Title: A Pivotal Phase 2 Trial of Ponatinib (AP24534) in Patients with Refractory Chronic Myeloid Leukemia and Ph+ Acute Lymphoblastic Leukemia

NCT Number: NCT01207440

Protocol Approve Date: 03 April 2015

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A Pivotal Phase 2 Trial of Ponatinib (AP24534) in Patients with Refractory Chronic Myeloid Leukemia and Ph+ Acute Lymphoblastic Leukemia

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Amendment 5 Protocol Version 6.0 – 03 April 2015

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Medical Monitor: PPD

Additional Contacts:

1 CONTACTS

1.1 Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESI)

Any death, serious adverse event (SAE), or adverse event of special interest (AESI) experienced by the patient from the time of signing the informed consent to 30 days of receiving the last dose of study drug, or any death, SAE, or AESI believed to be study drug-related that occurs more than 30 days after receiving study drug, must be promptly reported (within 24 hours) by telephone or facsimile to the Sponsor or the Sponsor's designee.

1.2 Contact for Emergencies and Study Related Issues

A list of the Sponsor's study personnel and their contact information is included in the Study Reference Manual(s).

2 APPROVAL

The protocol must be read before signing.

2.1 Investigator Signature

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

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

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

2.2 Sponsor Representative Signature

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

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

3 DISCLOSURE STATEMENT

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5 LIST OF ABBREVIATIONS

Abbreviation	Term
ADME	absorption, distribution, metabolism, excretion
AP	accelerated phase
AE	adverse event
ALL	acute lymphoblastic leukemia, also known as acute lymphocytic leukemia
AESI	adverse event of special interest
ALT	alanine aminotransferase
AML	acute myelogenous leukemia, also known as acute myeloid leukemia
ANC	absolute neutrophil count
ARIAD	ARIAD Pharmaceuticals, Inc.
ASCVD	atherosclerotic cardiovascular disease
ASO	allele-specific oligonucleotide
ASO qRT-PCR	allele-specific oligonucleotide quantitative reverse transcript-PCR
AST	aspartate aminotransferase
AUC	area under the curve
ß-HCG	beta-human chorionic gonadotropin
BM	bone marrow
BP	blast phase
BUN	blood urea nitrogen
CBC	complete blood count
CCyR	complete cytogenetic response
CFR	Code of Federal Regulations (USA)
CHR	complete hematologic response
CI	confidence interval
Cl	chloride
CLL	chronic lymphocytic leukemia
CML	chronic myelogenous leukemia, also known as chronic myeloid leukemia
CNS	central nervous system
CP	chronic phase
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
cTn	cardiac troponin
DDI	drug-drug interaction
DLT	dose-limiting toxicity
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECHO	echocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
FDA	Food and Drug Administration (United States)
FGFR	fibroblast growth factor receptor
GCP	Good Clinical Practice
GVHD	graft-versus-host disease

Abbreviation	Term
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	high density polyethylene
hERG	human ether-a-go-go related gene
HHT	homoharringtonine
HIV	human immunodeficiency virus
HPFB	Health Products and Food Branch (Canada)
HTN	hypertension
I	isoleucine
IC_{50}	50% inhibitory concentration
ICH	International Conference on Harmonisation
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
LDL	Low-density lipoprotein
LLD	lower limit of detection
LLT	lowest level term
LOD	limit of detection
LVEF	left ventricular ejection fraction
MDS	myelodysplastic syndrome
MaHR	major hematologic response
MedDRA	Medical Dictionary for Regulatory Activities Terminology
MCyR	major cytogenetic response
MI	myocardial infarction
MMR	major molecular response
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute (of the United States)
NCI CTCAE, v.4.0	NCI Common Terminology Criteria for Adverse Events, version 4.0
NEL	no evidence of leukemia
NIH	National Institutes of Health (of the United States)
NOAEL	No observed adverse effect level
PCR	polymerase chain reaction
PCyR	partial cytogenetic response
PDGFR	platelet-derived growth factor receptor
PFS	progression-free survival
P-gp	permeability glycoprotein
Ph	Philadelphia chromosome
Ph+	Philadelphia chromosome positive
PK	pharmacokinetic(s)
PT	prothrombin time

Abbreviation	Term
PTT	partial thromboplastin time
QD	every day (daily)
QTcF	QT interval corrected (Fridericia)
RBC	red blood cell
SAE	serious adverse event
SC	subcutaneous
SCT	stem cell transplant
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
$t_{1/2}$	half-life
T	threonine
TGA	Therapeutic Goods Administration (Australia)
TIA	transient ischemic attack
TKI	tyrosine kinase inhibitor
TLS	Tumor Lysis Syndrome
TRAE	treatment related adverse event
ULN	upper limit of normal
URL	upper reference limit
USA	United States of America
USAN	United States Adopted Name
VEGFR	vascular endothelial growth factor receptor
VOE	vascular occlusive event
WBC	white blood cell (count)

6 DEFINITION OF TERMS

Term	Definition
Active Study Period	The **active study period** for a patient begins with administration of the first dose of ponatinib and continues through 30 days following discontinuation of ponatinib.
Adverse Drug Reaction	An **adverse drug reaction** is any adverse event that is deemed to be at least possibly related to the study drug.
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-Trial	The **end-of-trial** (completion) date is when all patients have completed all study visits or have otherwise discontinued from the study.
Enrolled Patient	An **enrolled patient** is a patient who has signed the informed consent form, completed all screening evaluations, has been deemed eligible for the trial and for whom the enrollment procedure has been completed, and received first dose of ponatinib.
Ethics Committee	Throughout this document the term **Ethics Committee** (EC) refers to all appropriate properly constituted committees or boards recognized by the appropriate regulatory agencies for approving clinical studies. These include independent EC and Institutional Review Boards.
Evaluable for Efficacy	Any eligible patient who receives ponatinib is considered **evaluable for efficacy** analyses.
Evaluable for Safety	Any patient who receives ponatinib is considered **evaluable for safety analyses**.
Follow-up Period	The **follow-up period** for a patient begins at the end of the active study period (i.e., at the Follow-up Visit) and continues for not more than 24 months from the administration of the first dose of ponatinib.
Institutional Review Board	Throughout this document the term **Institutional Review Board** (IRB) refers to all appropriate properly constituted committees or boards recognized by the appropriate regulatory agencies for approving clinical studies. These include independent ECs and IRBs.

Term	Definition
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 (CFR, United States); the Good Clinical Practice (GCP): Consolidated Guideline (Canada); the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice; the Therapeutic Goods Administration Annotated International Conference on Harmonisation Guidelines (Australia); and the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Patients.
Regulatory Agency	Throughout this document the term **regulatory agency** refers to all appropriate health and regulatory agencies. These may be international, national, or local and may include but not be limited to the Australian Therapeutic Goods Administration (TGA), the Canadian Health Products and Food Branch (HPFB), the European Medicines Agency (EMA), and the United States Food and Drug Administration (FDA).
Screening Period	The **screening period** for a patient begins when the informed consent form is signed and continues until the first dose of study drug is administered.
Sponsor	Throughout this document the term **Sponsor** refers to all appropriate research departments within ARIAD Pharmaceuticals, Inc., or its designee.
Study Reference Manual/s	In the context of this study, **Study Reference Manual/s** is a general term for the information provided to sites on technical aspects of the trial.
Study Drug	A **study drug** is any drug, device, biological agent, or comparator (including placebo) used in the Sponsor's clinical research and development studies. For the purposes of this protocol, the study drug is ponatinib.

Term	Definition
Study Start Date	The **study start date** is the date that the first patient signs the informed consent form.

7 SYNOPSIS

Study Title	A Pivotal Phase 2 Trial of Ponatinib (AP24534) in Patients with Refractory Chronic Myeloid Leukemia and Ph+ Acute Lymphoblastic Leukemia
Clinical Phase	Phase 2
Study Rationale	**Introduction** AP24534 (United States Adopted Name [USAN]: ponatinib) is a novel synthetic orally-active tyrosine kinase inhibitor (TKI). Ponatinib was specifically developed to inhibit BCR-ABL, the fusion protein that is the product of the Philadelphia chromosome (Ph) in chronic myeloid leukemia (CML) and in a subset of acute lymphoblastic leukemia (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. The approved therapies for Ph positive (Ph+) disease work well. For example, there are 3 clinical trials of imatinib in untreated patients that provide prolonged follow-up of patients. The largest of these, the IRIS trial, demonstrates a 5-year overall survival of 89% (Druker, 2006). But, population studies suggest patients in community settings may fare worse. Lucas and colleagues (2008) report in their longitudinal series that 49% of patients initially treated with imatinib discontinued therapy because of either the development of resistance or intolerance at 24 months. Recently both dasatinib (Kantarjian et al, 2010) and nilotinib (Saglio et al, 2010) have been demonstrated to be superior to imatinib in terms of response rates; but, at this time, follow-up from these studies is too limited to estimate long-term failure rates. The treatments for CML have evolved over the course of the conduct of this phase 2 trial. At the time the trial was initiated, the only TKIs approved to treat CML or Ph+ ALL were imatinib, dasatinib, and nilotinib. During the course of the trial, bosutinib and ponatinib received marketing authorizations. Imatinib is used for the treatment of newly diagnosed CML patients in chronic phase (CP), or accelerated phase (AP), after failing interferon therapy, and nilotinib is now also approved for this indication. For the treatment of patients intolerant or resistant to prior therapy, including imatinib in the second line, both dasatinib and nilotinib are approved. Bosutinib is approved for CML patients who have experienced failure of prior therapy. Resistance to prior therapy is the major reason Ph+ patients suffer loss of disease control. The most important mechanism of resistance to TKI therapy is the evolution of mutations in BCR-ABL that render the protein product of the oncogene refractory to kinase inhibition. Ponatinib has been demonstrated to inhibit all mutations, in vitro, that it has been tested against and that arise during the development of resistance (O'Hare et al, 2009). Moreover, in a preclinical experiment formulated to assess the potential for emergence of additional mutations during ponatinib treatment, complete suppression of the development of resistant mutations was demonstrated. These characteristics support the testing of ponatinib in patients resistant to prior TKI therapy. The most common single resistant mutation is a transition point mutation at position 944 of the BCR-ABL gene, resulting in a substitution of isoleucine (symbol I) for threonine (T) at position 315 of the protein: designated T315I (Quintas-Cardama and Cortes, 2008). The T315I mutation accounts for 15%-20% of all mutants observed in refractory CML. Although dasatinib is effective against some mutations that confer resistance to imatinib therapy, and nilotinib also treats some imatinib-induced mutations, neither inhibit T315I; hence, there is no approved drug active against T315I. Ponatinib inhibits T315I. Other mutations confer resistance to both imatinib

	and dasatinib, such as F317L, while other mutations confer resistance to imatinib and nilotinib, such as E255V. Ponatinib inhibits these mutations, as well. A factor that contributes to therapeutic failure of the first or second generation agents is intolerance to therapy. Although the marketed drugs are convenient and safe, they cause adverse events (AEs) that result in dose reduction or even cessation of therapy in a proportion of patients. The side effect profile of imatinib includes edema, fluid retention, myelosuppression, cardiac toxicity, hepatotoxicity, and hemorrhage. Dasatinib is associated with severe myelosuppression, hemorrhage, fluid retention, effusions, and QT prolongation. Nilotinib is also associated with myelosuppression, QT prolongation, and sudden death. These AEs, and especially fluid retention and myelosuppression, lead to intolerance to continued therapy in a number of patients. In summary, while the approved therapies for Ph+ disease represent substantial progress, they fail in a significant proportion of patients because of either the development of resistance or intolerance. Thus, the need for new therapies is evident. This phase 2 pivotal trial of ponatinib completed enrollment in October 2011 and enrolled 449 patients. This amendment provides recommendations to investigators for dose reduction based on response, provides updated information on the risks of vascular occlusion, neuropathy, and cardiac failure and recommendations for management of these events, and adds a definition of overdose and guidance for reporting of overdose.

<table>
<tr><td>Study Objective(s)</td><td>Primary Objective:
To determine the efficacy of ponatinib in patients with CML in CP, AP or BP or with Ph+ ALL who either:
are resistant or intolerant to either dasatinib or nilotinib,
Or:
have the T315I mutation.
Secondary Objectives:
● To further characterize the anti-leukemia activity of ponatinib in these patients as evidenced by clinical responses, molecular responses, and clinical outcomes,
● To characterize the molecular genetic status of patients, and
● To examine the safety of ponatinib in these patients.</td></tr>
<tr><td>Trial Design</td><td>This is a multi-center, international, phase 2, single-arm, open-label trial of oral ponatinib in patients with Ph+ disease. Eligible patients will have CML in CP, AP, or BP as defined below, or Ph+ ALL. Patients will either 1) have disease resistant to, or be intolerant to, therapy with either dasatinib or nilotinib; or 2) have the T315I mutation of BCR-ABL. Patients will receive once daily oral administration of ponatinib at a dose of 45 mg. Patients will be assessed for hematologic response, cytogenetic response, and molecular response. Molecular genetic analyses will also be performed. Adverse events will be assessed throughout and categorized by the United States of America (USA) National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE, v.4.0) (see Attachment D). Patients will be evaluated according to the Schedule of Events in Section 8. Assessments will be according to standard international criteria. Patients will remain on treatment until disease progression or intolerance develops or they meet one or more of the criteria listed in Section 13.8. Progression-free survival and overall survival data will also be collected and analyzed. Patients will be grouped in the following cohorts:
<table>
<tr><th></th><th>Chronic Phase (CP)</th><th>Accelerated Phase (AP)</th><th>Blast Phase (BP)/Ph+ ALL</th></tr>
<tr><td>Resistant or intolerant to dasatinib or nilotinib</td><td>Cohort A</td><td>Cohort C</td><td>Cohort E</td></tr>
<tr><td>T315I mutation</td><td>Cohort B</td><td>Cohort D</td><td>Cohort F</td></tr>
</table>
Each of the 6 cohorts proposed in this trial are representative of distinct patient populations with different primary endpoints. Each cohort of patients will be analyzed separately for efficacy. The safety data from all cohorts will be pooled for the purpose of describing the safety of all treated patients as a whole. These cohorts can be viewed as 6 separate studies that are enrolled through this single “umbrella” protocol; therefore, no adjustments for multiplicity are planned.</td></tr>
</table>

Study Endpoints	**Primary Endpoint:** ● For CML patients in CP at study entry: major cytogenetic response (MCyR), defined as complete cytogenetic response (CCyR) or partial cytogenetic response (PCyR). CP patients in CCyR are **not** eligible for this study. ● For CML patients in AP at study entry: major hematologic response (MaHR), defined as complete hematologic response (CHR) or no evidence of leukemia (NEL). AP patients in MaHR are **not** eligible for this study. ● For CML patients in BP at study entry or Ph+ ALL patients: MaHR, consisting of CHR or NEL. BP and Ph+ ALL patients in MaHR are **not** eligible for this study. **Secondary Endpoints:** ● For CML patients in CP: - Hematologic responses: CHR; - Cytogenetic responses: confirmed MCyR; and - Molecular responses: major molecular response (MMR). ● For CML patients in AP or BP or Ph+ ALL patients: - Cytogenetic responses: CCyR, PCyR, confirmed MCyR; and - Molecular responses: MMR. ● For all patients: time to response, duration of response, progression-free survival, and overall survival. ● For all patients: safety and tolerability. **Exploratory Endpoints:** CCI [redacted]
Diagnosis and Main Criteria for Inclusion	1. Patients must have CML in any phase (CP, AP, or BP of any phenotype) or Ph+ ALL (defined in Sections 12.3 and 12.4). a. All patients must have screening bone marrow (BM) cytogenetics with conventional banding performed within 42 days prior to beginning treatment b. Examination of at least 20 metaphases is required. If less than 20 metaphases are examined, the BM aspirate should be repeated. Patients must either meet criterion 2 or 3: 2. Be previously treated with and resistant, or intolerant, to either dasatinib or nilotinib: 2.1 Resistance is defined for CML CP patients (CP 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: 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.

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 CML AP 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 a MaHR.

b. At any time after the initiation of therapy, the loss of a 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 a MaHR.

2.3 Resistance is defined for CML BP 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 a MaHR.

b. At any time after the initiation of therapy, the loss of a 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 a MaHR.

2.4 Intolerance to dasatinib or nilotinib 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) in the absence of a CCyR for CP patients or 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 manufacturer (80 mg daily [QD] for dasatinib;

400 mg QD for nilotinib) in 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), patients who have gone on to later line therapy are eligible having failed dasatinib or nilotinib.

OR

3. Develop the T315I mutation after any TKI therapy.

   3.1 Patients with T315I mutation after any TKI need not have been treated with dasatinib or nilotinib.

   3.2 Patients with T315I in CP must have less than a CCyR (> 0% Ph+).

   3.3 Patients with T315I in AP, BP, or Ph+ ALL must have less than a MaHR.

   3.4 Patients with any history of T315I mutation will be eligible for study participation. However, only those patients who carry a T315I mutation that is detected by direct sequencing in a pre-treatment blood sample using the study's central laboratory will be analyzed in the T315I subset. Details are provided in Section 12.5.

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

4. Must be ≥18 years old.
5. Provide written informed consent.
6. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
7. Minimum life expectancy of 3 months or more.
8. Adequate renal function defined as serum creatinine < 1.5 × upper limit of normal (ULN) for institution.
9. 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 (PT) < 1.5 × ULN.
10. Normal pancreatic status defined as:
    a. Lipase ≤ 1.5 × ULN for institution,
    b. Amylase ≤ 1.5 × ULN for institution.
11. Normal QTcF interval on screening electrocardiogram (ECG) evaluation, defined as QTcF of ≤ 450 ms in males or ≤ 470 ms in females.
12. For females of childbearing potential, a negative pregnancy test must be documented prior to enrollment.
13. Female and male patients who are of childbearing potential must agree to use an effective form of contraception with their sexual partners throughout participation in this study.
14. 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 1 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 hydroxyurea or anagrelide within 24 hours prior to receiving the first dose of ponatinib, 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 14 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, or vincristine within 7 days prior to the first dose of ponatinib, or received other chemotherapy within 14 days prior to the first dose of ponatinib. Otherwise, 2a applies. d. All patients are excluded if they have not recovered (> grade 1 by NCI CTCAE, v. 4.0) from AEs (except alopecia) due to agents previously administered. 3. Underwent autologous or allogeneic stem cell transplant < 60 days prior to receiving the first dose of ponatinib, any evidence of on-going graft versus-host disease (GVHD), or GVHD requiring immunosuppressive therapy. 4. Take medications that are known to be associated with Torsades de Pointes. These prohibited medications are listed in Attachment B. 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 CML CP are excluded if they are in CCyR. 8. Patients with CML AP, CML BP, or Ph+ ALL are excluded if they are in MaHR. 9. 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. 10. Have significant or active cardiovascular disease, specifically including, but not restricted to: a. Myocardial infarction within 3 months prior to first dose of ponatinib, c. History of clinically significant atrial arrhythmia or any ventricular arrhythmia, d. Unstable angina within 3 months prior to first dose of ponatinib, e. Congestive heart failure within 3 months prior to first dose of ponatinib. 11. Have a significant bleeding disorder unrelated to CML or Ph+ ALL.

	12. Have a history of pancreatitis or alcohol abuse. 13. Have uncontrolled hypertriglyceridemia (triglycerides > 450 mg/dL). 14. Have malabsorption syndrome or other gastrointestinal illness that could affect absorption of orally administered ponatinib. 15. 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). 16. Are pregnant or lactating. Women of childbearing potential must agree to effective contraception from the time of signing informed consent through the Follow-up Visit, approximately 30 days after last dose of ponatinib. 17. 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. 18. 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. 19. 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.
Approximate Number of Patients	The overall total enrollment will be approximately 450 patients.
Approximate Duration of Patient Participation	Each patient will undergo a period of up to 3 weeks for screening prior to treatment. The duration of therapy will be determined by the patient's response and toxicity. At a minimum, all patients benefiting from treatment will be followed for up to 24 months after first dose of ponatinib. After 24 months, patients can remain on ponatinib if continuing to benefit from treatment,
Approximate Number of Study Centers	Approximately 60 centers; multi-national.
Approximate Duration of Study	The estimated duration of the trial is approximately 8 years, including 12 months of enrollment. Patients will remain on treatment until they meet one or more of the criteria in Section 13.8.
Dosage and Administration	Ponatinib will be administered orally once daily at a dose of 45 mg per day. **Dose Reduction Recommendations Based on Response** • All CP-CML patients currently on trial who had already achieved MCyR had their dose reduced to 15 mg QD, 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 justified treatment with a higher dose. • All CP-CML patients currently on trial who had not yet achieved MCyR had their dose reduced to 30 mg QD, 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 justified treatment with a higher dose.

	• All AP-CML, BP-CML, and Ph+ ALL patients currently on trial had their dose reduced to 30 mg QD, 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 justified treatment with a higher dose. • All patients who lose response at a lower dose may have their dose escalated (up to a maximum of 45 mg QD) as long as the dose had not been previously lowered as a result of an adverse event. These dose reductions were implemented via direct communication to investigators in October 2013. For all patients, the dosing changes based on the above recommendations or the justification not to change the patient from his or her current dose should be documented in the patient's chart and in the study drug administration page of the electronic case report form (eCRF).
Concomitant Treatment	Medical or surgical treatment necessary for the patient's well-being is permitted. Management of known risk factors for cardiac disease, such as diabetes, hypertension, and hyperlipidemia should be optimized. **Prohibited 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 (see exclusion criteria 9). - Use of any other investigational drug or device. - Medications with a known risk of Torsades de Pointes (see Attachment B). - Herbal preparations or related over-the-counter preparations containing herbal ingredients (eg, St. John's Wort, Blue Cohosh, Estroven) either during or within 2 weeks prior to the first dose of ponatinib. - Elective surgery requiring in-patient care. Medications that are potent inhibitors or inducers of CYP3A4 (see Attachment C) should be avoided, but are not prohibited (see Section 15.3). Medications that prolong the QT interval without known risk of Torsades de Pointes should be avoided, but are not prohibited. If such medications are necessary, and used while a patient is on study, then additional ECG monitoring should be performed as clinically indicated. Where appropriate, patients may be treated with hematopoietic growth factors for limited times.
Efficacy Evaluation	Hematologic response rate, cytogenetic response rate, and disease progression will be assessed according to standard criteria. Refer to Attachment A for definition of response criteria.
Safety Evaluation	Safety assessments will include physical and laboratory examination. Adverse events will be graded according to the NCI CTCAE v 4.0. All patients receiving at least 1 dose of ponatinib will be considered evaluable for safety. The AE incidence rates, as well as the frequency of occurrence of overall

	toxicity, categorized by toxicity grades (severity), will be described for each cohort of the trial. Listings of laboratory test results will also be generated, and descriptive statistics summarizing the changes in laboratory tests over time will be presented.
Statistical Analysis	**Overview of Trial Design** This is a phase 2, single-arm trial in patients with CML and Ph+ ALL. Cohort A will consist of CP CML patients resistant or intolerant to dastinib or nilotinib. Cohort B will consist of CP CML patients with T315I mutations. Cohorts C and E will consist of AP and BP/Ph+ ALL patients, respectively, who are resistant or intolerant to dasatinib or nilotinib. Cohorts D and F will consist of AP and BP/Ph+, respectively, with the T315I mutation. Each of the 6 cohorts proposed in this trial are representative of distinct patient populations. Each cohort of patients will be analyzed separately for efficacy. The safety data from all cohorts will be pooled for the purpose of describing the safety of all treated patients as a whole. These cohorts can be viewed as 6 separate studies that are enrolled through a single "umbrella" protocol; therefore, no adjustments for multiplicity are planned. **Sample Size Determination: Cohorts A and B** The primary endpoint for this trial for patients with CP CML (Cohorts A and B) will be MCyR. The MCyR rate is defined as the proportion of patients who have achieved a CCyR or PCyR after the initiation of study treatment. The primary analysis of the primary endpoint of MCyR will be performed using a 2-sided exact 95% confidence interval (CI) for MCyR rate among all treated patients in each cohort. Data on the use of second generation TKIs in patients who have failed dasatinib and nilotinib are available in several small studies (Giles et al, 2007; Quintas-Cardama et al, 2007; Garg et al, 2009). These 3 studies demonstrate approximately 30% MCyR in these patients. However, these are highly selected patient populations; they do not include patients who have failed more than 2 agents, and responses are typically of short duration. Thus, for the purposes of this trial, the null or uninteresting MCyR rate is set at 20% for Cohort A (resistant and intolerant CP patients). The alternative MCyR rate is set at 35% for Cohort A. The overall alpha level for each cohort will be set at 0.05. With a cohort size of 100 patients, a minimum of 29 responders (ie, those with a CCyR and a PCyR) would need to be observed in Cohort A in order to observe an exact 95% CI such that the lower bound exceeds 20% and the upper bound exceeds 35%. Therefore, 100 patients will provide at least 85% power to distinguish between a null response rate of 20% and an alternative response rate of 35% in Cohort A. The study will also provide at least 98% power to distinguish between 20% and 40%, in which case 29 responses will also be required, and at least 78% power to distinguish between 30% and 45%, in which case 40 responses would be required. With a cohort size of 100 patients, the maximum width of the exact 95% CI will be approximately 20% when the MCyR rate is in the expected range of 20% to 35%. For Cohort B (T315I CP patients), the null or uninteresting MCyR rate is set at 10% and the alternative MCyR rate is set at 35%. Data on the use of second generation drugs (Muller et al, 2009; Garg et al, 2009) in these patients suggest that less than 10% of patients achieve MCyR. With a cohort size of 60 patients, a minimum of 14 responders would need to be observed in Cohort B in order to observe an exact 95% CI such that the lower bound exceeds 10% and the upper bound exceeds 35%. Therefore, 60 patients will provide approximately 98% power to distinguish between a null

	response rate of 10% and an alternative response rate of 35% in Cohort B. With a cohort size of 60 patients, the maximum width of the exact 95% CI will be 25% when the MCyR rate is in the expected range of 10% to 35%. **Sample Size Determination: Cohorts C-F** The sample sizes for Cohorts C to F (AP and BP/Ph+ ALL) are based on similar considerations for each cohort (Garg et al, 2009). The endpoint for these cohorts is MaHR. Major hematologic response rate is defined as the proportion of patients achieving a CHR or NEL response. The null or uninteresting MaHR rate is set at 10% and the alternative MaHR 30%. With a cohort size of 40 patients, a minimum of 9 responders would need to be observed in cohorts C to F in order to observe an exact 95% CI such that the lower bound exceeds 10% and the upper bound exceeds 30%. Forty patients in each cohort will provide approximately 89% power to distinguish between the null response rate of 10% and an alternative response rate of 30% in these cohorts. **Overall Sample Size Determination** For each disease phase, after the initiation of treatment, patients will be tested for the T315I mutation. Depending on the outcome of the test, patients will be assigned to a resistant/intolerant cohort (cohorts A, C or E, respectively, depending on disease phase) or a T315I cohort (cohorts B, D, or F). For example, a CP patient will be tested and assigned to cohort A or B, an AP patient will be assigned to cohorts C or D, and a BP or Ph+ ALL patient will be assigned to cohort E or F. Therefore, enrollment and assignment to the paired cohorts comprising a disease phase are linked by the relative prevalence of T315I patients and the T315I testing scheme. Early enrollment experience demonstrates that patients whose disease is resistant or intolerant to therapy are relatively more common than patients who carry the T315I mutation. Since the scientific objectives of the study require meeting accrual goals for the T315I cohorts (and, indeed, all cohorts), it is anticipated that the higher relative proportion of resistant/intolerant patients to T315I patients will require over-enrollment of the resistant/intolerant cohorts (A, C, and E) to ensure full T315I patient enrollment. Thus, overall total enrollment will be determined by the need to fill the T315I cohorts. At the time of this amendment, it is anticipated the trial may require up to 450 patients to ensure reaching the planned sample sizes of the T315I cohorts. Individual cohorts may be closed by the Sponsor to control overall enrollment to the study.
Rationale for Number of Patients	Approximately 450 patients will be enrolled in this study, to allow the T315I cohorts to enroll completely. See Section 19.1 for additional details.

8 SCHEDULE OF EVENTS

Table 8-1 Schedule of Events for CHRONIC PHASE (CP) PATIENTS*

CYCLE (1 cycle = 28 days)	Screening	Cycle 1				Cycle 2		Cycle 3			Cycles 4 to 13	End of Cycles 6,9,12	End of Cycles 15, 18, 21, 24, 27, 30, 33, 36, 39	End of Every Subsequent 6th Cycle
DAY	**-21 to 1[1]**	**1**	**8**	**15**	**22**	**1**	**15**	**1**	**15**	**28**	**1**	**28**	**28**	**28**
PROCEDURE														
Informed Consent[2]	X													
Medical/Surgical History & Demographics[3]	X													
Cancer Diagnosis & Prior Cancer Therapy[4]	X													
BCR-ABL Mutation History[5]	X													
Vital Signs[6]	X	X		X		X		X			X		X	X
Physical Exam including Hepatosplenomegaly & ECOG Performance Status[7]	X	X		X		X		X			X		X	X
Complete Blood Count (CBC) with Differential[8]	X	X	X	X	X	X	X	X	X		X		X	X
Serum Chemistry, Amylase, Lipase[9]	X	X		X		X	X	X	X		X		X	X
Serum Triglycerides[9]	X													
Fasting Cholesterol/Lipid Assessment[9]													X	X
HbA1c[9]													X	X
Prothrombin Time (PT)/PTT[10]	X													
Pregnancy[11]	X													
Electrocardiogram (ECG)[12]	X					X				X				
Echocardiogram (ECHO)[13]	X									X				
Adverse Events	THROUGHOUT STUDY													
Concomitant Medications	THROUGHOUT STUDY													
RESPONSE ASSESSMENT														
Bone Marrow (BM) Aspirate & Cytogenetic Response[14]	X									X		X	X[22]	X[22]
Molecular Response[15]	X									X		X	X	X
Additional Disease Assessments[16]	X									X		X	X	X
MUTATION ANALYSIS														
Direct Sequencing for T315I[17]	X													
EXPLORATORY TESTS														
CCI [redacted]														
CCI [redacted]														

*See notes following Table 8-2 and footnotes following Table 8-3.

Table 8-2 Schedule of Events for ACCELERATED PHASE (AP), BLAST PHASE (BP), AND Ph+ ALL PATIENTS*

CYCLE (1 cycle = 28 days)	Screening	Cycle 1					Cycle 2			Cycle 3			Cycles 4 to 26		End of Even Cycles 4 to 24	End of Cycles 27, 30, 33, 36, 39 and then Every Subsequent 6th Cycle
DAY	**-21 to 1[1]**	**1**	**8**	**15**	**22**	**28**	**1**	**15**	**28**	**1**	**15**	**28**	**1**	**15**	**28**	**28**
PROCEDURE																
Informed Consent[2]	X															
Medical/Surgical History & Demographics[3]	X															
Cancer Diagnosis & Prior Cancer Therapy[4]	X															
BCR-ABL Mutation History[5]	X															
Vital Signs[6]	X	X		X			X			X			X			X
Physical Exam including Hepatosplenomegaly & ECOG Performance Status[7]	X	X		X			X			X			X			X
Complete Blood Count (CBC) with Differential[8]	X	X	X	X	X		X	X		X	X		X	X		X
Serum Chemistry, Amylase, Lipase[9]	X	X		X			X	X		X			X			X
Serum Triglycerides[9]	X															
Fasting Cholesterol/Lipid Assessment[9]																X
HbA1c[9]																X
Prothrombin Time (PT)/PTT[10]	X															
Pregnancy[11]	X															
Electrocardiogram (ECG)[12]	X						X					X				
Echocardiogram (ECHO)[13]	X											X				
Adverse Events	THROUGHOUT STUDY															
Concomitant Medications	THROUGHOUT STUDY															
RESPONSE ASSESSMENT																
Bone Marrow (BM) Aspirate & Cytogenetic Response[14]	X					X			X						X	X[23]
Molecular Response[15]	X								X						X	X
Additional Disease Assessments[16]	X								X						X	X
MUTATION ANALYSIS																
Direct Sequencing for T315I[17]	X															
EXPLORATORY TESTS																
CCI [redacted]																
CCI [redacted]																

*See notes below and footnotes following Table 8-3.

Notes for both Schedule of Events Table 8-1 and Table 8-2:

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 bone marrow [BM] and pregnancy test below). Otherwise, samples or activities should occur **within 3 days** of the scheduled study day unless otherwise noted in 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.

Please pay special attention to tests required for **primary and secondary assessments:**

Chronic phase (CP) (Table 8-1):

Complete hematologic response (CHR): Hematologic response determination occurs for CP patients with each complete blood count (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 cycles up to Cycle 27. Any time after 27 cycles, patients who are not in CCyR continue to require a BM aspirate and cytogenetic assessment every 6 cycles through Cycle 39 and at least yearly thereafter (more frequent is acceptable if clinically indicated). Patients documented to be in CCyR after the BM aspirate and cytogenetic assessment at Cycle 27 (or later) are not required to have any further BM aspirates unless there is at least a 10-fold increase in BCR-ABL transcripts from the lowest point obtained on study and the patient is not currently in MMR, at which time BM aspirate and cytogenetics must be obtained. Bone marrow and cytogenetic assessments thereafter should be performed as clinically indicated based on the clinical situation and the results of the previous bone marrow cytogenetics. Patients who are in MMR any time after Cycle 27 are not required to have BM or cytogenetic assessments unless clinically indicated.

Any time a bone marrow aspirate is performed, 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 cycles up to Cycle 39, and subsequently every 6 cycles for the duration of the study.

Accelerated phase (AP), blast phase (BP), and Ph+ ALL (Table 8-2):

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 Cycle 1 Day 28, Cycle 2 Day 28, and at the end of each even-numbered cycle thereafter through Cycle 24, then at the end of Cycle 27. Any time after 27 cycles, patients who are not in CCyR continue to require a BM aspirate and cytogenetic assessment every 3 cycles until Cycle 39 and at least yearly thereafter (more frequent is acceptable if clinically indicated). Patients documented to be in CCyR and MMR after the BM aspirate and cytogenetic assessment at Cycle 27 (or later) are not required to have any further BM aspirates unless there is at least a 10-fold increase in BCR-ABL transcripts from the lowest point obtained on study and the patient is not in MMR, at which time BM aspirate and cytogenetics must be obtained. Bone marrow and cytogenetic assessments thereafter should be performed as clinically indicated based on the clinical situation and the results of the previous bone marrow cytogenetics. Patients who are in MMR any time after Cycle 27 are not required to have BM or cytogenetic assessments unless clinically indicated.

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 cycles through Cycle 24, then at the end of Cycle 27. Further need for BM aspirates beyond Cycle 27 are as described in the MaHR paragraph above. Any time a bone marrow aspirate is performed conventional banding for cytogenetics is required. More frequent assessments are allowed, but these are not required.

MMR: Collection of peripheral blood for determination of molecular response occurs every 2 cycles up to Cycle 24, every 3 cycles until Cycle 39, and subsequently every 6 cycles for the duration of the study. For BP and Ph+ ALL, a sample of marrow aspirate for molecular response is also collected, if a BM aspirate is performed.

Table 8-3 Schedule of Events for End-of-Treatment Visit, Follow-up Visit, and Survival Follow-up*

Procedure	Visit		Survival Follow-up[21]
	End-of-Treatment Visit[20]	Follow-up Visit[20]	
Vital Signs[6]	X	X	
Physical Exam including Hepatosplenomegaly & ECOG Performance Status[7]	X	X	
Complete Blood Count (CBC) with Differential[8]	X	X	
Serum Chemistry, Amylase, Lipase[9]	X	X	
Fasting Cholesterol/Lipid Assessment[9]	X		
Pregnancy Test (if applicable)[11]	X		
Electrocardiogram (ECG)[12]	X		
Echocardiogram (ECHO)[13]	X	X	
Adverse Events & Concomitant Medications	X	X	
RESPONSE ASSESSMENT			
Bone Marrow (BM) Aspirate & Cytogenetic Response[14]	X		
Molecular Response[15]	X		
MUTATION ANALYSIS			
Direct Sequencing for T315I[17]	X		
EXPLORATORY TESTS			
CCI			
CCI			
SURVIVAL FOLLOW-UP			
Survival[21]			X

*See footnotes below.

Footnotes for Schedule of Events Table 8-1, Table 8-2, and Table 8-3.

1. Screening tests and procedures are used to establish eligibility of the patient for the trial. All screening tests must be done **within 21 days** prior to the first dose of ponatinib with the exception of the screening bone marrow (BM) aspirate (within 42 days) and screening pregnancy test (within 7 days). Patients must continue to maintain laboratory values within eligibility perimeters if any given procedure or laboratory test is repeated prior the start of ponatinib on Cycle1, Day 1.
2. Informed consent, documented by a signed consent form, must be obtained prior to any screening activities not otherwise part of the patient's care.
3. Demographic information and medical and surgical history will be recorded. Demographic information consists of the patient's age, gender, race, and ethnicity (as allowed by local law and regulations).
4. Both the initial leukemia diagnosis and the current screening diagnosis must 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 or intolerance to each regimen. Stem cell transplant or experimental therapy history is also recorded.
5. At the time of screening, prior and current history of any known BCR-ABL mutations must be recorded (note: actual screening BCR-ABL mutation testing is covered in footnote 18).
6. Vital signs are temperature, pulse, respiratory rate, and blood pressure (when patient is seated). Height and weight are required only at screening.
7. A screening complete physical examination must be performed on Cycle 1, Day1 prior to the first administration of study drug. The extent of the physical examination should be consistent with the medical history and the patient's underlying disease. Subsequent physical examination may be directed to relevant findings in the patient. ECOG performance status should be evaluated during each physical examination. However, screening and directed physical examination in all patients need to assess for

hepatosplenomegaly. 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 examination. The End-of-Treatment Visit physical examination should be a complete physical examination. The Follow-up Visit physical examination may be directed to any relevant findings.

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

9. Serum Analysis

   a) Serum Chemistry, Amylase, 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), fasting glucose, albumin, creatinine, total bilirubin (direct and indirect), alanine aminotransferase (AST [SGOT]), aspartate aminotransferase (ALT [SGPT]), alkaline phosphatase, magnesium, phosphorous, calcium, amylase, and lipase. The full chemistry panel must be obtained as specified in the Schedule of Events (Table 8-1, Table 8-2, and Table 8-3) or more frequently as clinically indicated.

   b) Serum Triglycerides

   A fasting or non-fasting serum triglyceride level must be collected during screening. If a patient is ineligible based on a non-fasting level, the test may be repeated with a fasting level to determine eligibility.

   c) Fasting Cholesterol/Lipid Assessment

   Fasting serum cholesterol and lipid panel (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, HDL/LDL ratios, and triglycerides) must be collected as specified in the Schedule of Events (Table 8-1, Table 8-2, and Table 8-3) beginning with the patient's next scheduled visit. More frequent measurements may be required as clinically indicated.

   d) HbA1c

   Hemoglobin A1c (HbA1c) testing must be performed as specified in the Schedule of Events (Table 8-1, Table 8-2, and Table 8-3) beginning with the patient's next scheduled visit. More frequent measurements may be required as clinically indicated.

10. The prothrombin time (PT) may be expressed as an International Normalization Ratio (INR) or in seconds.

11. The pregnancy test must be a beta-human chorionic gonadotropin (β-HCG) test and either urine or serum can be used. Women who are not of childbearing potential (status post hysterectomy, status post-bilateral oophorectomy, or post-menopausal [defined as amenorrhea for at least 12 months]) do not need to have the test performed. The test must be known to be negative prior to the study drug administration and be **within 7 day**s prior to first study drug administration. Women of child-bearing potential at study start must also complete the pregnancy test at the End-of-Treatment Visit.

12. All electrocardiograms (ECGs) must be 12-lead ECGs. 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 calculating of QTc intervals and the QTcF interval must be normal on screening as specified in the eligibility criteria (Section 12.1). Additionally, 12-lead ECGs must be performed at the times specified in the Schedule of Events, or more frequently if clinically indicated. If other medications known to prolong the QTcF interval are used while a patient is on study, then additional ECG monitoring should be performed as clinically indicated.

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

14. 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 response of the patient as delineated in Attachment 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 should be repeated.

    Regardless of a patient's response status, a BM aspirate is required every 3 months for CP patients through the end of Cycle 27; and at the end of Cycle 1, Cycle 2, and then every 2 months until Cycle 24 and at the end of Cycle 27 for AP, BP and Ph+ ALL patients. For BM aspirate requirements after Cycle 27 for CP patients please refer to footnote 23 below and for BM aspirate requirements after Cycle 27 for AP, BP and Ph+ALL patients please refer to footnote 24 below.

    A BM aspirate is performed at the End-of-Treatment if it has been ≥ 12 weeks for CP and ≥ 8 weeks for AP or BP or Ph+ ALL since the last BM aspirate. See notes above for relation to response assessments. Bone marrow aspirates and biopsies may be performed at other times when clinically indicated. Results of any BM aspirate or biopsy, whether scheduled or unscheduled, must be recorded in the patient's electronic case report form (eCRF).

15. Samples of peripheral blood (in CP and AP) or peripheral blood and BM (in BP and Ph+ ALL) for molecular response (BCR-ABL transcript quantification) must be collected on these days. Specific instructions will be supplied in the Study Reference Manual.

16. 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.

17. BCR-ABL mutation testing of peripheral blood is required for participation in this trial. A sample must be collected and submitted during screening to document the type(s) of BCR-ABL mutations present at the time of screening. This screening sample will be used to identify patients with T315I mutations for later subset analysis. The sample must be submitted and documentation of receipt by the central laboratory received prior to the initiation of study drug treatment. Additional blood samples will be collected and stored for additional analyses of the T315I mutation. Specific instructions will be supplied in the Study Reference Manual.

18. CCI [redacted]

19. CCI [redacted]

20. The End-of-Treatment Visit should be performed within 2 weeks (14 days) of the patient's last dose of study drug or the investigator/patient decision to discontinue treatment, whichever occurs later. The Follow-up Visit will be conducted approximately 30 days (± 7 Days) after the last dose of study drug. For both the End-of-Treatment and Follow-up Visits, the information may be collected from tests that were performed for the study or as part of the patient's routine medical care.

21. Survival data will be collected every 12 weeks +/- 2 weeks starting after the last dose of study drug or the investigator/patient decision to discontinue treatment, whichever occurs later, and continuing for up to 96 months from the time the last patient is assigned to treatment. These data do not need to be obtained during a visit, and phone contact is acceptable.

22. Any time after 27 cycles, CP patients who are not in CCyR continue to require a BM aspirate and cytogenetic assessment every 6 cycles through Cycle 39, and at least yearly thereafter (more frequent is acceptable if clinically indicated). Patients documented to be in CCyR any time after the BM aspirate and cytogenetic assessment at Cycle 27 (or later) are not required to have any further BM aspirates unless there is at least a 10-fold increase in BCR-ABL transcripts from the lowest point obtained on study, and the patient is not currently in MMR, at which time BM aspirate and cytogenetic assessments must be obtained.

Subsequent BM aspirate and cytogenetic assessments should be performed as clinically indicated. Patients who are in MMR any time after Cycle 27 are not required to have BM aspirate or cytogenetic assessments unless clinically indicated.

23. Any time after 27 cycles, AP, BP and Ph+ ALL patients who are not in CCyR continue to require a BM aspirate and cytogenetic assessment every 3 cycles through Cycle 39, and at least yearly thereafter (more frequent is acceptable if clinically indicated). Patients documented to be in CCyR any time after the BM aspirate and cytogenetic assessment at Cycle 27 (or later) are not required to have any further BM aspirates unless there is at least a 10-fold increase in BCR-ABL transcripts from the lowest point obtained on study and the patient is not currently in MMR, at which time BM aspirate and cytogenetic assessments must be obtained. Subsequent BM aspirate and cytogenetic assessments should be performed as clinically indicated. Patients who are in MMR any time after Cycle 27 are not required to have BM aspirate or cytogenetic assessments unless clinically indicated.

9 INTRODUCTION

9.1 Background

AP24534 (United States Adopted Name [USAN]: ponatinib) is a novel, synthetic, orally-active multi-targeted tyrosine kinase inhibitor (TKI). The primary target for ponatinib is BCR-ABL, an abnormal tyrosine kinase that is the hallmark of chronic myeloid leukemia (CML) and Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL). Ponatinib was designed using the Sponsor's computational and structure-based drug design platform to inhibit the enzymatic activity of BCR-ABL with very high potency and broad specificity. The agent was intended to target not only native BCR-ABL, but also BCR-ABL isoforms that carry mutations that confer resistance to treatment with existing TKIs, including especially the T315I mutation for which no effective therapy exists. Preclinical data demonstrate that the compound inhibits the activity of all the isoforms tested, as well as the proliferation and survival (in vitro and in vivo) of cell lines expressing known BCR-ABL mutants that confer broad TKI resistance. Clinical data from an ongoing phase 1 trial also suggest clinical activity against resistant BCR-ABL mutants. Thus, ponatinib exhibits broad-spectrum inhibition of BCR-ABL mutants; it is a pan-BCR-ABL inhibitor. It is proposed to carry out pivotal clinical studies of ponatinib in CML and Ph+ ALL patients resistant or intolerant to therapy with either of the second generation approved TKIs, dasatinib or nilotinib, or who carry the T315I mutation.

Current Treatments for Chronic Myeloid Leukemia (CML) and Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ ALL)

Prior to the approval of the first TKI that targeted the BCR-ABL fusion oncoprotein, imatinib, studies of interferon therapy for CML resulted in approximately a 10% complete cytogenetic response (CCyR) rate and an approximately 57% 5-year survival (O'Brien et al, 2003). Treatment for CML was significantly advanced in 2001 following the approval of imatinib. Since then, targeted therapy with imatinib in the first line has become standard. Recent studies have demonstrated that both nilotinib (Saglio et al, 2010) and dasatinib (Kantarjian et al, 2010), second generation TKIs with improved potencies, are more effective therapies in untreated CML patients than imatinib. These drugs are both now approved in the first-line patient population.

Imatinib is an effective drug and in initial studies, the CCyR rate was reported as 76% (O'Brien et al, 2003). In recent comparison trials, nilotinib demonstrated a CCyR rate by 12 months of 80% versus 65% for imatinib (Saglio et al, 2010). Similarly, dasatinib exhibited a 77% confirmed CCyR rate compared with 66% for imatinib, with a minimum of 12 months of follow-up. Long term data from these studies are not yet available. However, at 7 years of follow-up from the initial imatinib studies, approximately 40% of patients discontinue therapy due to resistance or intolerance to this agent (Baccarani et al, 2009). Dasatinib and nilotinib also are approved for the treatment of patients who are or become resistant to imatinib therapy, ie, in the second line after imatinib failure. These drugs yield CCyR rates from 30% to 50% in this setting (Talpaz et al, 2006; Kantarjian et al, 2006). Thus, a sizable fraction of first- and second-line patients fail to achieve CCyR, and so, despite these major advances in treatment, resistance continues to be a significant challenge in the treatment of CML. Bosutinib is also now available for CML patients who have experienced failure of prior TKI therapy.

Despite these advances in therapy, resistance and intolerance continue to be a significant challenge in the treatment of CML.

The molecular biology of Ph+ ALL is similar to that of CML; thus, TKIs have been utilized in this condition as well. Historically, patients with Ph+ ALL have been treated with standard cytotoxic chemotherapy regimens; however, the results have been unsatisfactory with overall survival of approximately 40% (Kantarjian et al, 2008). Treatment with allogeneic hematopoietic stem cell transplantation (SCT) lowers the 5-year risk of relapse and increases event-free survival and overall survival in eligible patients (Gruber et al, 2009). However, allogeneic SCT is a limited treatment option. More recently, the TKI imatinib was demonstrated to improve complete responses during induction therapy in first line patients with Ph+ ALL over standard chemotherapy induction (Ottmann et al, 2007): imatinib is indicated for Ph+ ALL. Unfortunately, most often these results are not durable as resistance develops. Dasatinib is also indicated in the treatment of patients with Ph+ ALL who are resistant or intolerant to prior therapy. Data have emerged that demonstrate that many of these patients carry the T315I mutation resistant to all currently approved TKIs (Gruber et al, 2009).

The best understood mechanism of resistance to TKI therapy is the development of point mutations in BCR-ABL. More than 100 different mutations (such as T315I) in the kinase domain of ABL have been discovered and have been shown to be responsible for 40% to 50% of the resistance to existing TKIs (Jabbour et al, 2009). The detection of kinase domain mutations even early in disease is adversely prognostic (Khorashad et al, 2008), is higher in accelerated phase (AP)/blast phase (BP) compared with chronic phase (CP), and increases with the duration of disease (Quintas-Cardama and Cortes, 2008). For patients who fail imatinib therapy, the frequency of BCR-ABL mutations ranges from 40% to 90%, depending on the phase and method of detection (Quintas-Cardama and Cortes, 2008).

The most common single resistant mutation, which occurs in approximately 15% of patients who develop resistance to imatinib (Quintas-Cardama and Cortes, 2008), is a transition point mutation at position 944 of the BCR-ABL gene, resulting in a substitution of isoleucine (symbol I) for threonine (T) at position 315 of the protein: designated T315I. The T315I mutation accounts for 15%-20% of all mutants observed in refractory CML (Nicolini et al, 2009). Although dasatanib is effective against some mutations that confer resistance to imatinib therapy, and nilotinib also treats some imatinib-induced mutations, no approved drug inhibits T315I. Ponatinib, however, does inhibit T315I. Some mutations confer resistance to both imatinib and dasatanib, such as F317L, while other mutations confer imatinib and nilotinib resistance, such as E255V: ponatinib inhibits these mutations, as well.

As discussed above, there are currently no approved therapies for patients with the T315I mutation (Nicolini et al, 2009). In a recent study of second generation agents used in resistant patients, no cytogenetic responses in patients with the T315I mutation were observed (Garg et al, 2009), in keeping with the known lack of efficacy of existing drugs against this mutation. Another study examined patients carrying characterized mutations treated with dasatinib, and in this series, 2 of 21 patients with the T315I mutation experienced partial cytogenetic responses (PCyR), but no CCyR (Muller et al, 2009). Several investigational agents have been or are currently in development against this gatekeeper mutation. The agent that is furthest along in development is omacetaxine mepesuccinate, a semisynthetic formulation of the cytotoxic plant alkaloid homoharringtonine (HHT), which is administered subcutaneously (SC) daily.

The mechanism of action by which HHT exerts its antitumor activity is through inhibition of protein synthesis and promotion of apoptosis (Quintas-Cardama et al, 2009a). Omacetaxine is not a TKI, and does not specifically interact with BCR-ABL carrying the T315I mutation. Data on 44 patients with CML and the T315I mutation were presented (25 CP, 11 AP, 8 BP). In CP patients, complete hematologic response (CHR) rate was 80%, and the CCyR rate was reported as 16%, with a major cytogenetic response (MCyR) rate of 20%. These data on omacetaxine suggest a modest cytogenetic response rate using this agent, but only in the limited subset of patients carrying the T315I mutation.

There are a variety of methods available to detect BCR-ABL kinase domain point mutations, including direct sequencing, polymerase chain reaction (PCR)-based methods including allele-specific variants, and denaturing high-performance liquid chromatography. Direct sequencing typically detects mutations when they are present in 10% to 30% of circulating BCR-ABL transcripts (Baccarani et al, 2009). Direct (Sanger) sequencing has been considered the standard test for mutation detection, as was recommended by a panel of experts at a National Institutes of Health (NIH) consensus conference in late 2005 (Hughes et al, 2006). It was used, for example, uniformly in the study of Muller and colleagues (2009) cited above to determine mutation status in all patients treated with dasatinib. Allele-specific methods can detect much lower levels of BCR-ABL transcripts. These are the 2 most important detection methods. In this clinical trial, the T315I + population is defined on the basis of the ability to detect the T315I mutation with direct sequencing. Allele-specific oligonucleotide (ASO) testing for the T315I mutation will be performed.

Minimal data exist on treatment of the broader patient population who has failed second generation agents, ie, the population not limited to the T315I mutants. Garg and colleagues at MD Anderson, cited above, conducted a single institution study of 1 second-generation agent (dasatinib or nilotinib) used as therapy in 48 patients who failed the alternative second-generation treatment (Garg et al, 2009). The patient population included a variety of resistant mutations. This study reports a 32% CCyR rate in CP patients, but only half of these CCyR were sustained beyond 12 months. Giles et al. (2007; 2010) reported their experience using nilotinib in patients who failed imatinib and then dasatinib. In their study (Giles et al, 2010), they studied 39 CP and 21 AP patients. Most patients (67% in CP) were intolerant, and not resistant, to prior therapy. They reported a 16 MCyR (41%) in all CP patients. Quintas-Cardama et al. (2007) reported results using dasatinib after nilotinib failure in 23 patients, but in these patients (mostly AP or BP) responses (26%) were more often partial (4 PCyR) than complete (2 CCyR), and were of short duration.

Taken together, the above data 1) suggest that existing second generation agents have minimal activity in the third line, with modest MCyR rates of short duration, 2) suggest that omacetaxine has limited activity confined to the T315I patient population, and 3) underscore the need for a TKI with activity against the broad spectrum of resistant mutants including, but not limited to, T315I.

Recently, updated standard recommendations for the management of CML, as formulated by European Leukemia Net, were published (Baccarani et al, 2009). Leading CML experts reviewed the relevant data and literature on CML therapy and promulgated consensus approaches to defining responses, recommending monitoring strategies, and providing a therapeutic algorithm that accounts for such emerging data as summarized above.

In brief, therapy recommendations comprise imatinib in the first line; for imatinib failures, second line dasatinib or nilotinib, or allogeneic SCT for AP/BP patients and those who carry the T315I mutation; and for dasatinib or nilotinib failures, allogeneic transplant is also available. Allogeneic transplant is a limited option, available only to patients with excellent performance status with an appropriate donor. Apart from SCT, there is no agreed standard of care for patients who fail a second generation drug, or for patients who carry the T315I mutation.

This protocol will test ponatinib in the patient population defined by the experts cited above, ie, patients who are resistant or intolerant to either dasatinib or nilotinib, or who carry the T315I mutation after any TKI therapy.

9.2 Preclinical Pharmacology Studies

A preclinical development program has been completed to support the clinical development of ponatinib. Studies conducted to examine the nonclinical pharmacologic and pharmacodynamic activity of ponatinib (O'Hare et al, 2009) are summarized below.

In vitro kinase assays demonstrated that ponatinib inhibits native BCR-ABL and all 5 mutants tested, including T315I, with 50% inhibitory concentration (IC_{50}) of 0.37 to 2.0 nM. Ponatinib also inhibited the activity of other TKIs in vitro with IC_{50} < 10 nM including members of the SRC, vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR) and platelet-derived growth factor receptor (PDGFR) families (Table 9-1).

Table 9-1 Kinase Inhibition Profile of Ponatinib for Native ABL, ABL^{T315I}, and Selected Kinases

Kinase	IC_{50} (nM)
ABL	0.37
ABL^{T3151}	2.0
ABL^{Q252H}	0.44
ABL^{Y253F}	0.30
ABL^{M351T}	0.30
ABL^{H396P}	0.34
c-SRC	5.4
LYN	0.24
c-KIT	12.5
VEGFR2	1.5
FGFR1	2.2
PDGFRα	1.1
IR	>1000
IGF-1R	>1000
Aurora A	>1000
CDK2/Cyclin E	>1000

In cellular assays, ponatinib inhibited proliferation of Ba/F3 cells expressing native BCR-ABL and all 14 clinically relevant mutants tested, including T315I, with IC_{50} of 0.5 to 36 nM (Table 9-2). Ponatinib also inhibited the phosphorylation of BCR-ABL, as well as the direct BCR-ABL substrate CrkL. In assays using primary cells derived from CML patients with T315I mutant BCR-ABL, ponatinib inhibited cell growth, colony formation and levels of phosphorylated CrkL.

Table 9-2 Ponatinib IC_{50} Values for Ba/F3 Cellular Proliferation Assays and CML and Non-CML Cellular Proliferation Assays

	Ba/F3 Cell Proliferation Assay IC_{50} (nM)			
BCR-ABL	**Ponatinib**	**Imatinib**	**Nilotinib**	**Dasatinib**
Native	0.5	260	13	0.8
M244V	2.2	2000	38	1.3
G250E	4.1	1350	48	1.8
Q252H	2.2	1325	70	3.4
Y253F	2.8	3475	125	1.4
Y253H	6.2	>6400	450	1.3
E255K	14	5200	200	5.6
E255V	36	>6400	430	11
T315A	1.6	971	61	125
T315I	11	>6400	>2000	>200
F317L	1.1	1050	50	7.4
F317V	10	350	nd	53
M351T	1.5	880	15	1.1
F359V	10	1825	175	2.2
H396P	1.1	850	41	0.6
Parental	1713	>6400	>2000	>200

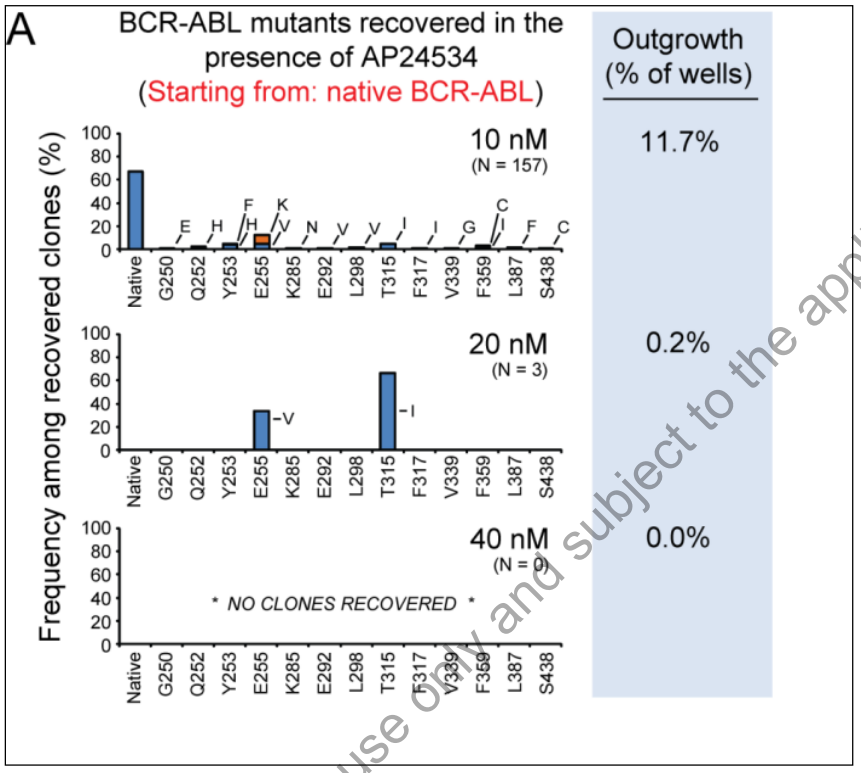
O'Hare T. et al (2005) Cancer Res. 65: 4500-4505
O'Hare T. et al (2007) Blood. 110: 2242-2249
O'Hare T. et al (2009) Cancer Cell. 16: 401-412

Ba/F3 cells expressing T315I BCR-ABL were used to test the antitumor activity of ponatinib in vivo. In a xenograft model, in which cells were injected SC, significant inhibition of tumor growth occurred with daily oral dosing of ponatinib at doses of > 10 mg/kg. Inhibition of BCR-ABL and CrkL phosphorylation was observed in tumors from mice treated with ponatinib. In a survival model, in which cells were injected intravenously, daily oral administration of ponatinib significantly improved survival at doses as low as 5 mg/kg. Ponatinib also improved survival significantly when Ba/F3 cells expressing native BCR-ABL were injected.

To identify mutations that may confer resistance to ponatinib a mutagenesis screen was performed using Ba/F3 cells expressing native BCR-ABL. This screen has successfully identified clinically relevant mutations that confer resistance to other BCR-ABL inhibitors (Bradeen et al, 2006). When the selection was performed in the presence of 40 nM ponatinib, outgrowth of resistant clones was suppressed completely (Figure 9-1). Thus, by this assessment, ponatinib appears to be a pan-BCR-ABL inhibitor. Since exposure of cells to 40 nM suppressed the emergence of any resistant mutants, and since this concentration had potent activity against

all individual mutants tested in Ba/F3 cells, including T315I, 40 nM can be considered a target efficacious trough concentration.

Figure 9-1 Single-Agent Ponatinib (AP24354) Completely Suppresses Resistant Outgrowth in Cell-Based Mutagenesis Screens



(A) Resistant clones recovered from ENU-treated Ba/F3 cells starting from native BCR-ABL cultured with graded concentrations of ponatinib (10, 20, 40 nM). Each bar represents the relative percentage of the indicated BCR-ABL kinase domain mutant among recovered subclones. Since the percentage of surviving resistant subclones and the concentration of ponatinib are inversely related, a different number of sequenced subclones are represented in the graph for each concentration of ponatinib. The percent of wells surveyed that contained outgrowth is indicated to the right of each graph.

In summary, these studies demonstrate ponatinib is an orally-active multi-target TKI that inhibits, with high potency, native BCR-ABL and all mutants tested.

In vitro and in vivo absorption, distribution, metabolism, and excretion (ADME) studies have been performed to understand the pharmacokinetics (PK) and metabolism of ponatinib. Ponatinib was bioavailable after oral administration to mice, rats and cynomolgus monkeys. The absolute bioavailability after an oral dose was 18.2% and 20.6%, respectively, in rats and monkeys. The blood clearance of ponatinib was low, approximately 17% of the hepatic blood flow in both rats and monkeys. The steady state volume of distribution (V_{ss}) was large, indicating that ponatinib was extensively distributed in extravascular compartments. The terminal half-life ($t_{½}$) after an intravenous (IV) dose was 10.2 and 5.3 hours, respectively, in rats and monkeys.

In vitro, ponatinib was very highly bound to plasma proteins (>99%) of mice, rats, monkeys and humans, and did not show preferential partitioning into red blood cells (RBCs) in whole blood.

Ponatinib is most likely to be a permeability glycoprotein (P-gp) substrate based on the Caco-2 model.

In vitro, ponatinib was metabolized to mainly AP24567 (N-desmethyl metabolite), and to a lesser extent to AP24734 (N-oxide). There were other mono-oxygenated metabolites whose contribution to the overall metabolism was insignificant. CYP3A4 was the major Cytochrome P450 isozyme responsible for the metabolism of ponatinib. In rat and monkey plasma also AP24567 and AP24734 were the principal metabolites. In mouse plasma, AP24567 was found to be a major metabolite.

Ponatinib is a substrate of CYP3A4, and is an inhibitor of CYPs 3A4, 2D6, and 2C19. It is likely that ponatinib might cause drug-drug interaction (DDI) with CYP3A4 inhibitors and substrates of CYPs 3A4/5, 2D6, and 2C19.

Overall, the metabolism of ponatinib in rats and monkeys (both in vivo and in vitro) was qualitatively similar to the metabolism of ponatinib in human liver microsomes and hepatocytes. All human in vitro metabolites were also present in the toxicological species, rat and monkey.

9.3 Preclinical Toxicology Studies

The safety of ponatinib has been investigated in laboratory animals and in in vitro systems. These investigations included single oral dose toxicology studies in mice, rats and cynomolgus monkeys, as well as 28-day and 6-month oral dose toxicology studies in rats and cynomolgus monkeys. In addition, the mutagenic potential of ponatinib was evaluated in an in vitro reverse mutation assay, an in vitro chromosomal aberration assay, and in an in vivo micronucleus test in mice. A safety pharmacology program was also completed to determine the potential effects of ponatinib on the nervous, renal, pulmonary, gastrointestinal, and cardiovascular systems. Cardiovascular evaluations included in vitro effects on the human ether-a-go-go related gene (hERG) and an in vivo study in conscious telemetered dogs.

The rat was shown to be the most sensitive species to the toxicologic effects of ponatinib based on both single dose and multiple dose regimens. Rats tolerated single oral doses of 10 mg/kg with mortality occurring at single oral doses of 30 mg/kg and greater. Mice tolerated single oral doses of 500 mg/kg and cynomolgus monkeys tolerated single oral doses of 45 mg/kg (the highest dose tested). In the 28-day oral toxicology study rats did not tolerate dose levels of 3 and 6 mg/kg with death/moribundicity occurring in 11 and 24% of the animals, respectively. In addition, 1 death occurred in the low dose group of 1.5 mg/kg/day on the last day of the dosing period for which a drug-related cause of death could not be ruled out. In the 28-day oral toxicity study in cynomolgus monkeys, an oral dose of 5 mg/kg/day was not tolerated, with mortality/moribundicity occurring in 3 of 10 animals during the last 2 weeks of the study. Histologic pancreatic changes observed in monkeys at the 5 mg/kg/day dose level included acinar cell necrosis, fibrosis and atrophy with a corresponding elevation in serum lipase level. The low- (1 mg/kg/day) and mid- (2.5 mg/kg/day) dose levels were tolerated by the monkeys with the exception of a mid-dose animal who appeared in poor physical condition toward the end of the dosing period.

In the 6-month oral toxicology study in rats, the no observed adverse effect level (NOAEL) was 0.25 mg/kg/day. Higher dose levels of 0.75 and 2 mg/kg/day caused mortality of some animals, and decreased body weight and food consumption relative to control. Histologic examination revealed decreased numbers of chondrocytes along the physis in the femur at the 0.75 and 2 mg/kg/day dose levels, and lymphoid depletion was observed in the thymus at the 2 mg/kg/day dose level. The observation in the femur appears to be species specific since it was not observed in the nonhuman primate studies. Another histologic observation in the 6-month rat study was a higher frequency and severity of chronic progressive nephropathy in the 2 mg/kg/day dose group in comparison with the vehicle control and lower dose group observations. Chronic progressive nephropathy is a normal age-related finding in rats; however, the higher incidence and severity of this observation in the high dose group suggests a drug-related exacerbation of this normal occurrence. Because chronic progressive nephropathy is a rodent specific entity, the observation of a chemically-related exacerbation is routinely regarded as having no relevance for extrapolation in human risk assessment. The administration of ponatinib to cynomolgus monkeys for 6 months at oral dose levels of 0.25, 0.75 and 2 mg/kg/day was well-tolerated with no ponatinib-related microscopic findings being observed at any dose level.

Ponatinib was shown to be non-mutagenic in the 3 mutagenicity assays that were performed, and the drug was shown to have a favorable safety pharmacology profile.

9.4 Clinical Studies

9.4.1 Overview of Ponatinib Phase 1

ARIAD Protocol AP24534-07-101 is a phase 1 clinical trial of oral ponatinib. The trial is a non-randomized, multi-center, dose-escalation study to evaluate the safety, tolerability, maximum tolerated dose (MTD), and biologic properties of ponatinib in patients with hematologic malignancies.

Enrollment for this study closed in October 2010. At the time of writing, the trial was ongoing; data as of 06 January 2014 are presented. A total of 81 patients with CP-CML, AP-CML, BP-CML, Ph+ ALL, and other hematologic malignancies who had no other effective treatment options enrolled in the study. A total of 65 patients had Ph+ leukemia (that is, CML or Ph+ ALL), 12 patients had AML, and 4 patients had other hematologic malignancies. Twenty-four patients remain on study (all CP-CML), with a minimum duration of follow-up of approximately 37 months for these remaining patients. Doses of 2, 4, 8, 15, 30, 45, and 60 mg were evaluated. Dose limiting toxicity of pancreatitis-related events was reported at 60 mg; therefore, the maximum tolerated dose and recommended phase 2 dose was determined to be 45 mg.

Substantial anti-tumor activity of ponatinib was observed (Cortes et al, 2012). The results are illustrated in Table 9-3 below (a more detailed presentation of treatment responses is provided in the Investigator's Brochure).

Table 9-3 Ponatinib Phase 1 Clinical Trial (AP24534-07-101): Best Response to Ponatinib Treatment in Ph+ Disease

Best Response	CP-CML n=43	AP-CML, BP-CML, Ph+ ALL n=22
Hematologic		
CHR*, n (%)	42 (98)	N/A
MaHR, n (%)	N/A	8 (36)
Cytogenetic		
MCyR, n (%)	31 (72)	7 (32)
CCyR, n (%)	32 (49)	4 (18)
Molecular		
MMR, n (%)	22 (51)	2 (9)

Data extraction date: 06 January 2014. CP-CML=chronic phase chronic myeloid leukemia; AP-CML=accelerated phase chronic myeloid leukemia; BP-CML=blast phase chronic myeloid leukemia; Ph+ ALL=Philadelphia chromosome positive acute lymphoblastic leukemia; CHR=complete hematologic response; MaHR=major hematologic response; MCyR=major cytogenetic response; CCyR=complete cytogenetic response; MMR=major molecular response. *Includes patients with new CHRs and patients who entered with CHR at baseline and maintained it.

The most common treatment-emergent AEs (≥30%) were rash (48.1%), nausea (45.7%), abdominal pain (44.4%), fatigue (44.4%), headache (42%), arthralgia (39.5%), constipation (39.5%), vomiting (38.3%), hypertension (37.0%), oedema peripheral (35.8%), platelet count decreased (35.8%), and pyrexia (35.8%).

Vascular occlusive events (VOEs, thrombotic and ischemic AEs) were identified as important adverse events with longer term treatment. These events include arterial events involving the cardiovascular, cerebrovascular, or peripheral vascular body systems, as well as venous thromboembolic events.

Serious VOEs occurred in 19 patients (23%): 11 patients (14%) had cardiovascular SAEs, 4 patients (5%) had cerebrovascular SAEs, 4 patients (5%) had peripheral vascular events, and 2 patients (2%) had venous SAEs. Some patients had events of more than one type. Vascular occlusive SAEs occurring in more than one patient were myocardial infarction/acute myocardial infarction (4 patients; 5%), troponin increased (3 patients; 3.7%), cerebrovascular accident (2 patients; 2.5%), peripheral arterial occlusive disease (2 patients; 2.5%), and peripheral ischemia (2 patients; 2.5%). A more detailed presentation of AEs is provided in the Investigator's Brochure.

The phase 1 data demonstrate that ponatinib has substantial activity in refractory CML in all phases, as well as in Ph+ ALL. The promising efficacy in phase 1 was the basis for the phase 2 clinical trial of ponatinib in CML and Ph+ ALL.

9.4.2 Update of Data from This Ongoing Trial (AP24534-10-201)

The safety and efficacy data from this trial have been used to support marketing applications in various jurisdictions. Data from this trial have been published (Cortes et al, 2013).

This trial enrolled 449 patients. Patients were enrolled in one of 6 cohorts depending on their disease type (CP-CML, AP-CML, or BP-CML/Ph+ ALL) and whether they had the T315I mutation of BCR-ABL. Response rates for the various cohorts are presented in Table 9-4.

Table 9-4 Ponatinib Phase 2 Clinical Trial (AP24534-10-201) by Cohort: Best Response to Therapy: Treated Population

	CP-CML			AP-CML			BP-CML, Ph+ ALL		
	Total N=267	**Cohort A CP/R-I N=203**	**Cohort B CP/T315I N=64**	**Total N=83**	**Cohort C AP/R-I N=65**	**Cohort D AP/T315I N=18**	**Total BP-CML, Ph+ ALL N=94**	**Cohort E BP, Ph+ ALL/R-I N=48**	**Cohort F BP, Ph+ ALL/ T315I N=46**
Hematologic, n (%)[a]	**N=267**	**N=203**	**N=64**	**N=83**	**N=65**	**N=18**	**N=94**	**N=48**	**N=46**
CHR[a]	250 (93.6)	192 (94.6)	58 (90.6)	N/A	N/A	N/A	N/A	N/A	N/A
MaHR	N/A	N/A	N/A	47 (56.6)	37 (56.9)	10 (55.6)	32 (34.0)	17 (35.4)	15 (32.6)
Cytogenetic, n (%)[b]	**N=267**	**N=203**	**N=64**	**N=83**	**N=65**	**N=18**	**N=94**	**N=48**	**N=46**
MCyR	149 (55.8)	104 (51.2)	45 (70.3)	32 (38.6)	22 (33.8)	10 (55.6)	29 (30.9)	13 (27.1)	16 (34.8)
CCyR	124 (46.4)	82 (40.4)	42 (65.6)	20 (24.1)	14 (21.5)	6 (33.3)	23 (24.5)	11 (22.9)	12 (26.1)
PCyR	25 (9.4)	22 (10.8)	3 (4.7)	12 (14.5)	8 (12.3)	4 (22.2)	6 (6.4)	2 (4.2)	4 (8.7)
Molecular, n (%)[c]	**N=267**	**N=203**	**N=64**	**N=83**	**N=65**	**N=18**	**N=94**	**N=48**	**N=46**
MMR	102 (38.2)	65 (32.0)	37 (57.8)	17 (20.5)	11 (16.9)	6 (33.3)	11 (11.7)	9 (18.8)	2 (4.3)

Source: AP24534-10-201 Table 14.2.4.1 (Cytogenetic and hematologic), Table 14.2.7.1 (MMR). Data extraction date 06 January 2014.
[a] Hematologic response is defined as CHR for Cohorts A and B, and as MaHR (CHR or no evidence of leukemia) for Cohorts C-F.
[b] Patients entering the study in PCyR must achieve a CCyR to be considered as having met MCyR criteria.
[c] Patients for whom a valid baseline MMR assessment is missing or who met the criteria for MMR at baseline were analyzed as non-responders.
CP-CML= chronic phase chronic myeloid leukemia, AP-CML= accelerated phase chronic myeloid leukemia, BP-CML= blast phase chronic myeloid leukemia, Ph+ ALL =acute lymphocytic leukemia, N/A = Not applicable; CHR=complete hematologic response; MaHR=major hematologic response; MCyR=major cytogenetic response; CCyR=complete cytogenetic response; PCyR=partial cytogenetic response; MMR=major molecular response.

The most common treatment-emergent AEs (≥30%) were thrombocytopenia (38%), constipation (37%), headache (37%), dry skin (35%), and abdominal pain (31%). The most common treatment-related AEs (≥20%) were platelet count decreased (38%), rash (35%), dry skin (32%), and abdominal pain (23%). The overall rate of VOEs was 20%, including cardiovascular (9%), cerebrovascular (6%), peripheral vascular (6%), and venous thromboembolic (5%).

Treatment-emergent vascular occlusive SAEs were reported in 14% of patients overall, which included: cardiovascular (6%), cerebrovascular (4%), peripheral vascular (4%), and venous thromboembolic (3%), with some patients experiencing more than one type of event.

A more detailed discussion of the results of this study is provided in the Investigator's Brochure.

9.4.3 Multivariate Analyses of Data from the Phase 2 Clinical Trial (AP24534-10-201, PACE)

Multivariate analyses were performed on data from this trial to evaluate the relationships between dose intensity and efficacy, and between dose intensity and safety.

A significant relationship was found between dose intensity and the occurrence of ≥ grade 3 serious adverse events including vascular occlusion, thrombocytopenia, pancreatitis, neutropenia, rash, increased ALT, increased AST, increased lipase, and myelosuppression in CML patients treated with ponatinib. In general, increasing dose intensity correlated with an increased probability of experiencing adverse events. Factors associated with a lower probability of adverse events were younger age, less time since diagnosis, and fewer prior TKIs.

With longer follow-up and the accumulation of VOEs, the relationship between dose intensity and vascular occlusive and arterial occlusive events was further examined using multivariate analysis with an expanded set of covariates with a minimum of 24 months of follow-up. All modeling showed a statistically significant association between dose intensity (up to the time of the events) and an increase in event rate in univariate models; this relationship became more significant when adjusting for covariates in multivariate models. These results are consistent with univariate analyses demonstrating relationships between a variety of historical risk factors, including prior myocardial infarction or coronary disease, diabetes mellitus, hypertension, and hypercholesterolemia, and the occurrence of vascular complications.

Increasing dose intensity is associated with higher response rates, but response rates are sufficiently high that it is reasonable to attempt to identify prospectively and with greater resolution the effect of lower starting doses. However, preliminary analyses in patients with AEs suggest that patients can maintain response on doses lower than 45 mg. Data from the phase 2 trial demonstrate that patients who achieved response, either at 45 mg or 30 mg, maintained responses after dose reduction to 30 mg or 15 mg because of adverse events. The maintenance of response appears to be independent of the length of dose reduction.

Taken together, the data suggest that measures to lower exposure, such as dose reduction, may reduce risk while maintaining response rates.

10 OBJECTIVES

The primary objective of this study is:

1. To determine the efficacy of ponatinib in patients with CML in chronic, accelerated or blast phase or with Ph+ ALL who are either:

   - resistant or intolerant to either dasatinib or nilotinib,

   or

   - have the T315I mutation.

The secondary objectives of this study are:

1. To further characterize the anti-leukemia activity of ponatinib in these patients as evidenced by clinical responses, molecular responses, and clinical outcomes;
2. To characterize the molecular genetic status of patients; and
3. To examine the safety of ponatinib in these patients.

11 TRIAL DESIGN

11.1 Structure

This is a multi-center, international, phase 2, single-arm, open-label trial of oral ponatinib in patients with Ph+ disease. Eligible patients will have CML in CP, AP, or BP as defined, or Ph+ ALL. Patients will either 1) have disease resistant to, or be intolerant to, therapy with either dasatinib or nilotinib; or 2) have the T315I mutation of BCR-ABL. Patients will receive once daily oral administration of ponatinib tablet at a dose of 45 mg. Patients will be assessed for hematologic response, cytogenetic response, and molecular response. Molecular genetic analyses will also be performed. Adverse events will be assessed throughout and categorized by NCI CTCAE v, 4.0. Patients will be evaluated according to the Schedule of Events tables in Section 8. Assessments will be according to standard international criteria. Patients will remain on treatment until disease progression or intolerance develops. Progression-free survival (PFS) and overall survival data will also be collected and analyzed. Patients will remain on treatment until they meet one or more criteria for withdrawal as listed in Section 13.8.

Patients will be grouped into cohorts as shown in Table 11-1.

Table 11-1 Patient Cohorts

	Chronic Phase (CP)	Accelerated Phase (AP)	Blast Phase (BP)/Ph+ ALL
Resistant or intolerant to dasatinib or nilotinib	Cohort A	Cohort C	Cohort E
T315I mutation	Cohort B	Cohort D	Cohort F

11.2 Study Endpoints

The primary endpoint of the study is:

1. For CML patients in CP at study entry: major cytogenetic response (MCyR), defined as complete cytogenetic response (CCyR) or partial cytogenetic response (PCyR).

   CP patients in CCyR are **not** eligible for this study.

2. For CML patients in AP at study entry: major hematologic response (MaHR), defined as complete hematologic response (CHR) or no evidence of leukemia (NEL).

   AP patients in MaHR are **not** eligible for this study.

3. For CML patients in BP at study entry or Ph+ ALL patients: MaHR, consisting of CHR or NEL.

   BP and Ph+ ALL patients in MaHR are **not** eligible for this study.

The secondary endpoints of the study are:

1. For CML patients in CP:
   a. Hematologic responses: CHR;
   b. Cytogenetic responses: confirmed MCyR; and
   c. Molecular responses: major molecular response (MMR).
2. For CML patients in AP or BP or Ph+ ALL patients:
   d. Cytogenetic responses: CCyR, PCyR, confirmed MCyR; and
   e. Molecular responses: MMR.
4. For all patients: time to response, duration of response, progression free survival, and overall survival.
5. For all patients: safety and tolerability.

The exploratory endpoints of the study are:

CCI

[redacted]

12 SELECTION OF STUDY POPULATION

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

Each patient's participation in the trial begins with the signing and dating of the informed consent form. Patients must meet the inclusion and exclusion criteria to be enrolled in the trial.

12.1 Inclusion Criteria

1. Patients must have CML in any phase (CP, AP, or BP of any phenotype) or Ph+ ALL (defined in Sections 12.3 and 12.4).
    a. All patients must have screening bone marrow (BM) cytogenetics with conventional banding performed within 42 days prior to initiating treatment.
    b. Examination of at least 20 metaphases is required. If less than 20 metaphases are examined, the BM aspirate should be repeated.

Patients must either meet criterion 2 or 3:

2. Be previously treated with and resistant, or intolerant, to either dasatinib or nilotinib:
    2.1 Resistance is defined for CML CP patients (CP 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: 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.
        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 CML AP patients (defined 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 a MaHR.
        b. At any time after the initiation of therapy, the loss of a 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 a MaHR.

2.3 Resistance is defined for CML BP patients (defined 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 a MaHR.

b. At any time after the initiation of therapy, the loss of a 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 a MaHR.

2.4 Intolerance to dasatinib or nilotinib 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) in the absence of a CCyR for CP patients or 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 manufacturer (80 mg QD for dasatinib; 400 mg QD for nilotinib) in 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), patients who have gone on to later line therapy are eligible having failed dasatinib or nilotinib.

OR

3. Develop the T315I mutation after any TKI therapy.

3.1 Patients with T315I mutation after any TKI need not have been treated with dasatinib or nilotinib.

3.2 Patients with T315I in CP must have less than a CCyR (>0% Ph+).

3.3 Patients with T315I in AP, BP, or Ph+ ALL must have less than a MaHR.

3.4 Patients with any history of T315I mutation will be eligible for study participation. However, only those patients who carry a T315I mutation that is detected by direct sequencing in a pre-treatment blood sample using the study's central laboratory will be analyzed in the T315I subset. Details are provided in Section 12.5.

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

4. Patients must be ≥ 18 years old.

5. Provide written informed consent.

6. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.

7. Minimum life expectancy of 3 months or more.
8. Adequate renal function defined as serum creatinine < 1.5× upper limit of normal (ULN) for institution.
9. Adequate hepatic function defined as:
    a. Total bilirubin <1.5 × ULN,
    b. Alanine animotransferase (ALT [SGPT]) and aspartate aminotransferase (AST [SGOT]) < 2.5 × ULN for institution (< 5 x ULN if liver involvement with leukemia),
    c. Prothrombin time (PT) < 1.5 × ULN.
10. Normal pancreatic status defined as:
    a. Lipase ≤ 1.5 × ULN,
    b. Amylase ≤ 1.5 × ULN.
11. Normal QTcF interval on screening ECG evaluation, defined as QTcF of ≤ 450 ms in males or ≤ 470 ms in females.
12. For females of childbearing potential, a negative pregnancy test must be documented prior to enrollment.
13. Female and male patients who are of childbearing potential must agree to use an effective form of contraception with their sexual partners throughout participation in this study.
14. Ability to comply with study procedures, in the Investigator's opinion.

12.2 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 1 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 hydroxyurea or anagrelide within 24 hours prior to receiving the first dose of ponatinib, 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 14 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, or vincristine within 7 days prior to the first dose of ponatinib, or received other chemotherapy within 14 days prior to the first dose of ponatinib. Otherwise, 2a applies.

d. All patients are excluded if they have not recovered (> grade 1 by NCI CTCAE, v. 4.0) from AEs (except alopecia) due to agents previously administered.

3. Underwent autologous or allogeneic stem cell transplant < 60 days prior to receiving the first dose of ponatinib; any evidence of on-going graft-versus-host disease (GVHD), or GVHD requiring immunosuppressive therapy.
4. Take medications that are known to be associated with Torsades de Pointes. These medications are listed in Attachment B.
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. Patient with CML CP are excluded if they are in CCyR.
8. Patients with CML AP, BP, or Ph+ ALL are excluded if they are in MaHR.
9. 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.
10. Have significant or active cardiovascular disease, specifically including, but not restricted to:
    a. Myocardial infarction within 3 months prior to first dose of ponatinib,
    b. History of clinically significant atrial arrhythmia or any ventricular arrhythmia,
    c. Unstable angina within 3 months prior to first dose of ponatinib,
    d. Congestive heart failure within 3 months prior to first dose of ponatinib.
11. Have a significant bleeding disorder unrelated to CML or Ph+ ALL.
12. Have a history of pancreatitis or alcohol abuse.
13. Have uncontrolled hypertriglyceridemia (triglycerides >450 mg/dL).
14. Have malabsorption syndrome or other gastrointestinal illness that could affect absorption of orally administered ponatinib.
15. 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).
16. Are pregnant or lactating. Women of childbearing potential must agree to effective contraception from the time of signing informed consent through the Follow-up Visit, approximately 30 days after last dose of ponatinib.
17. 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.

18. 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.

19. 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.

12.3 Classification of Chronic Myeloid Leukemia (CML) Patients

Patients with CML who enroll in the trial will be classified according to Talpaz and colleagues in their studies of dasatinib (Talpaz et al, 2006). See Table 12-1 below.

Table 12-1 Chronic Myeloid Leukemia (CML) Phase Classification

CML Phase	Criteria
Chronic Phase (CP)	<15% blasts in peripheral blood or bone marrow **and** <20% basophils in peripheral blood **and** <30% blasts + promyelocytes in peripheral blood or bone marrow **and** ≥100 x 10^9 platelets/L in peripheral blood **and** No extramedullary disease
Accelerated Phase (AP)	≥15% and <30 % blasts in peripheral blood or bone marrow **or** ≥20% basophils in peripheral blood or bone marrow **or** ≥30% blasts + promyelocytes in peripheral blood or bone marrow (but < 30% blasts) **or** <100 x 10^9 platelets/L in peripheral blood unrelated to therapy **or** Cytogenetic, genetic evidence of clonal evolution **And** No extramedullary disease
Blast Phase (BP)	≥30% blasts in peripheral blood or bone marrow **or** Extramedullary disease other than hepatosplenomegaly

12.4 Philadelphia Positive Acute Lymphoblastic leukemia (Ph+ ALL) 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.

12.5 CCI

CCI

[redacted]

CCI

Direct (Sanger) sequencing is the standard test for mutation detection, as was recommended by a panel of experts at an NIH consensus conference in late 2005 (Hughes et al, 2006). Direct sequencing can detect any potential single or compound mutation in BCR-ABL that is present in a sufficient percentage of transcripts (Muller et al, 2009). Patients who demonstrate the T315I mutation by this assay, irrespective of prior treatments, will be included in one of the T315I cohorts (depending on their stage of disease) for analysis. T315I patients, and thus the T315I cohorts, will therefore be defined as those in whom the T315I mutation is detected by direct sequencing.

It is possible that some patients with a history of T315I mutation will not demonstrate a detectable mutation at the time of trial entry. One potential explanation for this may be the well-described fall in the levels of T315I-containing CML clones, to below the limit of detection of the direct sequencing assay, when the selective pressure of TKI therapy is relaxed (Quintas-Cardama et al, 2008). Such patients (T315I- but T315I history+) will fall into one of 2 groups: those treated with only imatinib, and those treated with dasatinib or nilotinib. Patients who have been treated with dasatinib or nilotinib will be enrolled and assigned to one of the resistant/intolerant cohorts, as they meet the protocol eligibility criteria for this group irrespective of the absence of the T315I mutation. Patients who have been treated with imatinib only, however, would only be eligible if they carry a detectable mutation. Nonetheless, these patients will be offered study treatment as their history of T315I mutation renders them unlikely to benefit from existing therapies. But, they will not be included in the T315I cohorts (A, C, or E) as they do not meet the study-specified definition of a T315I carrier. Based on our phase 1 experience, we project that a small number of patients will have a T315I history, but will not be negative for T315I by the direct sequencing assay result.

Since all patients who meet all eligibility criteria apart from the T315I determination will receive study drug, treatment initiation will be allowed once documentation is received by the central laboratory of receipt of the direct sequencing blood sample. Determination of inclusion in the T315I cohorts will be required prior to the first assessment of the primary endpoint, to avoid the introduction of bias in cohort assignment.

All patients will also undergo ASO qRT-PCR during screening. This exploratory test is specific for T315I and is characterized by a 10-fold to 100-fold lower limit of detection (LLD) (ie, higher sensitivity) for the T315I mutation than the direct sequencing method (Deininger et al, 2006). It will be utilized in an exploratory analysis to determine the presence of T315I mutations below the level of detection (LOD) of the direct sequencing method, and the extent to which these mutations contribute to resistance and patient outcomes.

The schema for testing and assignment to treatment cohorts is illustrated in Figure 12-1.

Figure 12-1 Schema for T315I Mutation Testing

12.6 Number of Patients

At the time of this amendment, it is anticipated that approximately 450 patients will be enrolled in this study, to allow the T315I cohorts to enroll completely. See Section 19.1 for additional details.

12.7 Screening 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.

13 STUDY PROCEDURES

See Section 8, Schedule of Events, for the procedures to be performed at each visit.

Patients are considered "on-study" beginning with the signing of the informed consent form. The "active study period" begins with administration of the first dose of ponatinib and continues through 30 days following discontinuation of ponatinib (ie, at the Follow-up Visit) (see Section 6: Definition of Terms).

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

1. **Vital signs**

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

2. **Physical Examination**

   Following the physical examination for Cycle 1, Day 1, all subsequent physical examinations may be directed to relevant findings in the patient.

All physical examination should address the presence or absence of hepatosplenomegaly. In patients with extramedullary involvement, the site(s) of involvement must always be assessed.

3. **Complete Blood Count (CBC) with Differential**

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

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

The PT may be expressed as an International Normalized Ratio (INR) or in seconds.

5. **Serum Analysis**

a) Serum Chemistry, Amylase, 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), fasting glucose, albumin, creatinine, total bilirubin (direct and indirect), alanine aminotransferase (AST [SGOT]), aspartate aminotransferase (ALT [SGPT]), alkaline phosphatase, magnesium, phosphorous, calcium, amylase, and lipase. The full chemistry panel must be obtained as specified in the Schedule of Events (Table 8-1, Table 8-2, and Table 8-3) or more frequently as clinically indicated.

b) Serum Triglycerides

A fasting or non-fasting serum triglyceride level must be collected during screening. If a patient is ineligible based on a non-fasting level, the test may be repeated with a fasting level to determine eligibility.

c) Fasting Cholesterol/Lipid Assessment

Fasting serum lipid cholesterol and lipid panel (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, HDL/LDL ratios, and triglycerides) total, HDL, LDL) including triglycerides must be collected at the patient's next visit for those who did not have fasting levels at screening and at subsequent time points as specified in the Schedule of Events (Table 8-1, Table 8-2, and Table 8-3) beginning with the patient's next scheduled visit. More frequent measurements may be required as clinically indicated.

d) HbA1c

Hemaglobin A1c (HbA1c) testing must be performed as specified in the Schedule of Events (Table 8-1, Table 8-2, and Table 8-3) beginning with the patient's next scheduled visit. More frequent measurements may be required as clinically indicated.

6. **Pregnancy Test**

The pregnancy test must be a beta-human chorionic gonadotropin (β-HCG) test and either urine or serum can be used. Women who are not of childbearing potential (status

post-hysterectomy, status post-bilateral oophorectomy, or postmenopausal [defined as amenorrhea for at least 12 months]) do not need to have the test performed. The test must be known to be negative prior to the study drug administration and be performed within 7 days prior to first study drug administration. Women of child bearing potential at study start must also complete the pregnancy test at the End-of-Treatment Visit.

7. **Electrocardiogram (ECG)**

All ECGs must be 12-lead ECGs. 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 calculating of QTc intervals. Additionally, 12-lead ECGs must be performed at the times specified in the Schedule of Events, or more frequently if clinically indicated. If other medications known to prolong the QTcF interval are used while a patient is on study, then additional ECG monitoring should be performed as clinically indicated.

8. **Echocardiogram (ECHO)**

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

9. **Adverse Events (AEs) and Concomitant Medications**

Adverse events and concomitant medications are to be recorded continuously throughout the entire study.

10. **Bone Marrow (BM) Aspirate/Cytogenetics**

The BM aspirate results must list the components required for assessing response of the patient. Bone marrow aspirates and biopsies may be performed at other times when clinically indicated. Results of any BM aspirate or biopsy, whether scheduled or unscheduled, should be recorded in the patient's electronic case report form (eCRF). All BM examination must include blast count and cytogenetic assessment by conventional banding.

Bone marrow cytogenetics requires examination of at least 20 metaphases. If less than 20 metaphases are examined, the BM aspirate should be repeated.

For assessment of MCyR for CP patients, a BM aspirate for morphology and cytogenetics occurs every 3 cycles up to Cycle 27. Any time after 27 cycles, CP patients who are not in CCyR continue to require a BM aspirate and cytogenetic assessment every 6 cycles through Cycle 39, and at least yearly thereafter (more frequent is acceptable if clinically indicated). Patients documented to be in CCyR after the BM aspirate and cytogenetic assessment at Cycle 27 (or later) are not required to have any further BM aspirates unless there is at least a 10-fold increase in BCR-ABL transcripts from the lowest point obtained on study, and the patient is not currently in MMR, at which time BM aspirate and cytogenetic assessments must be obtained. Subsequent BM aspirate and cytogenetic assessments should be performed as clinically indicated.

Patients who are in MMR any time after Cycle 27 are not required to have BM aspirate or cytogenetic assessments unless clinically indicated. Any time a bone marrow aspirate is performed, conventional banding for cytogenetics is required. More frequent aspirates are allowed, but these are not required.

For assessment of MCyR for AP, BP and Ph+ ALL patients, a BM aspirate is required Cycle 1 Day 28, Cycle 2 Day 28, and at the end of each even-numbered cycle thereafter through Cycle 24, then at the end of Cycle 27. Any time after 27 cycles, patients who are not in CCyR continue to require a BM aspirate and cytogenetic assessment every 3 cycles through Cycle 39, and at least yearly thereafter (more frequent is acceptable if clinically indicated). Patients documented to be in CCyR any time after the BM aspirate and cytogenetic assessment at Cycle 27 (or later) are not required to have any further BM aspirates unless there is at least a 10-fold increase in BCR-ABL transcripts from the lowest point obtained on study and the patient is not currently in MMR, at which time BM aspirate and cytogenetic assessments must be obtained. Subsequent BM aspirate and cytogenetic assessments should be performed as clinically indicated. Patients who are in MMR any time after Cycle 27 are not required to have BM aspirate or cytogenetic assessments unless clinically indicated.

For assessment of MCyR for AP, BP and Ph+ ALL patients, a BM aspirate for morphology and cytogenetics occurs on Cycle 1 Day 28, Cycle 2 Day 28, and then every 2 cycles through cycle 24, then at the end of Cycle 27. Further need for BM aspirates beyond Cycle 27 are as described in the MaHR paragraph above. Any time a bone marrow aspirate is performed conventional banding for cytogenetics is required. More frequent assessments are allowed, but these are not required.

For MMR assessment for BP and Ph+ ALL, a sample of marrow aspirate for molecular response is also collected if a BM aspirate is performed.

A BM aspirate is performed at End of Treatment if it has been ≥12 weeks for CP and ≥8 weeks for AP, BP, or Ph+ALL since the last BM aspirate.

11. **Additional Disease Assessments**

Additional examination, laboratory studies, or imaging must be performed as appropriate to fully assess disease status. This might include documentation of hepatosplenomegly, or in patients with extramedullary involvement, imaging of the site(s) of involvement.

12. **BCR-ABL T315I Mutation Detection by Direct Sequencing**

Blood sample is required for BCR-ABL T315I mutation testing of peripheral blood by the Sanger direct sequencing method at screening and at the End-of-Treatment Visit. The result of this test is used for eligibility, and will be reported to the participating investigator. Additional samples will be collected and stored for additional T315I analyses. Specific instructions will be supplied in the Study Reference Manual.

13. **BCR-ABL Molecular Response Assessment**

Testing of peripheral blood (in all patients) or BM (in BP and Ph+ ALL patients) by quantitative real time PCR of the BCR-ABL transcript must be done at screening; during the treatment period at the same time as BM aspirates; and at the End-of-Treatment.

This test quantifies molecular response to therapy, and will be reported to the participating investigator. For assessment of molecular response for CP patients, collection of peripheral blood for determination of molecular response occurs every 3 cycles up to Cycle 39, and subsequently every 6 cycles for the duration of the study. For AP, BP and Ph+ALL patients, collection of peripheral blood for determination of molecular response occurs every 2 cycles up to Cycle 24, every 3 cycles until Cycle 39, and subsequently every 6 cycles for the duration of the study. For MMR assessment for BP and Ph+ ALL, a sample of marrow aspirate for molecular response is also collected if a BM aspirate is performed. Specific instructions will be supplied in the Study Reference Manual.

14. **BCR-ABL T315I Mutation Detection by Allele-Specific Oligonucleotide (ASO) Testing**

Blood sample is required for BCR-ABL T315I mutation testing of peripheral blood by quantitative ASO method at screening and at the End-of-Treatment. This test is exploratory, and the result of this test is not used for eligibility. Specific instructions will be supplied in the Study Reference Manual.

15. **Molecular Genetic Assessment**

Peripheral blood for molecular genetic testing is to be collected for analysis of molecular determinants of response or resistance to ponatinib that are present at the initiation of study treatment, or that develop during study treatment. This test is exploratory. Molecular genetic assessment must be done at screening; during the treatment period at the same time as BM aspirates (ie, at least 3 three months for CP and at least every 2 months for AP, BP, and Ph+ ALL); and at the End-of-Treatment. After Cycle 39, a separate molecular genetic sample is not required as the molecular genetic assessments may be performed using the molecular response sample (number 14 above). Specific instructions will be provided in the Study Reference Manual.

13.2 Screening

The following describes the procedures/tests required at screening (refer to Table 8-1 and Table 8-2).

Please note: Screening tests and procedures are used to establish eligibility of the patient for the trial. Patients must continue to maintain laboratory values within eligibility perimeters if any given procedure or laboratory test is repeated prior to the start of study drug on Cycle1, 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.
  - Demographic information consists of the patient's age, gender, race, and ethnicity (as allowed by local law and regulations).
- 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 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
- ECOG performance status
- CBC with differential
- Serum chemistry including amylase and lipase
- Serum triglycerides
- PT/ PTT
- Pregnancy test
- ECG (within the 21-day screening window)
- ECHO
- AEs and concomitant medications
- BM aspirate/cytogenetics
  - 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.
- Additional disease assessments (eg, evaluation of extramedullary disease sites, in AP, BP and Ph+ ALL)
- BCR-ABL mutation detection by Direct Sequencing
  - BCR-ABL mutation testing of peripheral blood is required for participation in this trial. A sample must be collected and shipped to the central laboratory during screening to document the type(s) of BCR-ABL mutations present at the time of screening. This screening sample will be used to identify patients with the T315I mutation. The sample must be submitted and documentation of receipt recorded by the central laboratory prior to a patient beginning treatment with ponatinib. However, the results of the test need not be available to initiate study drug administration. Results should be available within approximately 5 business days of receipt of sample by the central laboratory and before the end of Cycle 1. Additional blood samples will be collected and stored for additional analyses of the T315I mutation. Specific instructions will be supplied in the Study Reference Manual.
- BCR-ABL T315I mutation detection by ASO testing
- Molecular response assessment (quantitative PCR of BCR-ABL transcripts)
- Molecular genetics assessment

13.3 Active Study Period

Procedures to be performed during the study and timing of procedures are listed by disease state in Section 8 (refer to Table 8-1 and Table 8-2) and described in detail in Section 13.0.

Please maintain a special awareness of the assessments of the primary and secondary endpoints. These are discussed in the notes accompanying Tables 8-1 and 8-2.

13.4 Study Drug Administration

Study drug (ponatinib) will be self-administered by the patient. The starting dose will be 45 mg taken orally once daily. Each 28-day dosing period is referred to as 1 cycle. Patients will take the prescribed number of tablets with water, with or without food, at approximately the same time each day.

In October 2013 dose adjustments were made based on response to minimize the risk of adverse events with ponatinib while maintaining response:

- All CP-CML patients currently on trial who had already achieved MCyR had their dose reduced to 15 mg QD, 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 justified treatment with a higher dose.
- All CP-CML patients currently on trial who had not yet achieved MCyR had their dose reduced to 30 mg QD, 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 justified treatment with a higher dose.
- All AP-CML, BP-CML, and Ph+ ALL patients currently on trial had their dose reduced to 30 mg QD, 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 justified treatment with a higher dose.
- All patients who lose response at a lower dose may have their dose escalated (up to a maximum of 45 mg QD) as long as the dose had not been previously lowered as a result of an adverse event.

These dose reductions were implemented via direct communication to investigators. For all patients, the dosing changes based on the above recommendations or the justification not to change the patient from his or her current dose should be documented in the patient's chart and in the study drug administration page of the electronic case report form (eCRF).

13.5 Management of Missed Doses of Study Drug

Patients who forget to take their scheduled dose of study drug more than 6 hours after it is due should not make up the missed dose. Any missing doses should be recorded, and subsequent training of patients should be documented in the appropriate source record (eg, clinic chart), patient diary card, and study drug administration eCRF.

13.6 End-of-Treatment Visit

Study procedures at the End-of-Treatment Visit are to be conducted within 2 weeks following the last dose of ponatinib or the patient/investigator decision to end treatment, whichever is later (refer to Table 8-3).

The following are the procedures/tests required at the End-of-Treatment Visit:

- Vital signs
- Physical examination
  - The End-of-Treatment Visit physical examination should be a complete physical examination.
- ECOG performance status
- CBC with differential
- Serum chemistry including amylase and lipase
- Fasting cholesterol/lipid assessment
- ECG
- ECHO
  - An ECHO is necessary at the End-of-Treatment only if abnormality develops during the trial.
- Pregnancy test, if applicable
- BCR-ABL mutation detection by direct sequencing
- BCR-ABL T315I mutation detection by ASO testing
- Molecular response assessment
- Molecular genetic assessment
- AEs and concomitant medications

13.7 Removal of Patients from Study Drug Administration or Assessment

In the event that a patient is being considered to be withdrawn from the study, every effort will be made by the Investigator to discuss the circumstances regarding the permanent discontinuation from the study with the Sponsor's Medical Monitor first, and if the patient is discontinued, document and report the reasons for withdrawal as thoroughly as possible. The reason(s) for termination must be clearly reported on the appropriate page of the patient's eCRF. An eCRF must be completed for any patient who receives study drug. An End-of-Treatment reason must be recorded for any patient who receives study drug and/or is enrolled in the study.

If a patient is discontinued from the trial for any reason, every effort must be made to perform all clinical and laboratory procedures as scheduled for the End-of-Treatment Visit. In the event that the patient fails to return for the necessary visit(s), an effort must be made to contact the patient to determine the reason, and this information should be recorded in the appropriate source record and the end-of-treatment eCRF.

13.8 Criteria for Discontinuation

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

- Intolerable toxicity as determined by the Investigator;

- Myocardial infarction, stroke, or urgent revascularization, unless the benefit of study drug is believed to outweigh the risk, as determined by the investigator;
- Progression of disease requiring an alternate therapy, in the opinion of Investigator;
- Entry into another therapeutic clinical trial or start of additional anticancer therapy;
- Significant deviation from the protocol or eligibility criteria, in the opinion of the medical monitor or Investigator;
- Noncompliance with study or follow-up procedures;
- Patient withdrawal of consent and decision to discontinue participation;
- Termination of the trial by the sponsor;
- Any other reason that, in the opinion of the Investigator, would justify removal of the patient from the study.

13.9 Follow-up Visit

The Follow-up Visit will be performed approximately 30 days (± 7 days) after the last dose of Study Drug. The following procedures/tests are required at the Follow-up Visit or the patient/investigator decision to end treatment, whichever is later (refer to Table 8-3):

- Vital signs
- Physical examination
  - The Follow-up Visit physical examination may be directed to any relevant findings.
- ECOG performance status
- CBC with differential
- Serum chemistry with amylase and lipase
- ECHO
  - An ECHO is necessary at the Follow-up Visit only if an abnormality develops during trial.
- AEs and concomitant medications

13.10 Survival Follow-up

Survival data will be collected every 12 weeks ± 2 weeks starting after the last dose of study drug or the investigator/patient decision to discontinue treatment, whichever occurs later, and continuing for up to 96 months from the time the last patient is assigned to study treatment. These data do not need to be obtained during a visit, and phone contact is acceptable.

14 STUDY DRUG

14.1 Study Drug Administration

Study drug will be administered only to eligible enrolled patients at the participating centers listed on the FDA Form 1572. Patients do not need to continuously meet the eligibility criteria in order to continue on study drug.

14.2 Monitoring of Study Drug Administration

Patients will take the prescribed number of tablets with water, with or without food, at approximately the same time each day. Patients will be provided a diary card or equivalent where the date of administration will be recorded; complete instructions will be provided with the Study Reference Manual. Patients who forget to take their dose more than 6 hours after it is due should not make up the missed dose. Any missing doses should be recorded, and subsequent training of patients should be documented in the appropriate source record (eg, clinic chart). When possible, patients should take the study drug under observation during scheduled study visits to the clinic.

14.3 Supportive Care

An analysis of baseline risk factors in patients from this phase 2 study assessed the impact of hypertension, hypercholesterolemia, diabetes, and obesity, and revealed several risk factors that pre-dispose patients to vascular occlusive events (VOEs) on ponatinib (see Section 9.4.3). Based on this analysis, the following supportive care recommendations are provided to decrease the risk of VOEs for patients taking ponatinib.

Diabetes Treatment

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

Hypertension Treatment

Hypertension (HTN) may contribute to risk of vascular occlusive events. Patients who have HTN should be managed appropriately. During ponatinib treatment, blood pressure elevations should be monitored and managed. Hypertension should be treated to achieve a goal of < 150/90 mmHg. Initial antihypertensive treatment should generally include a thiazide-type diuretic, calcium channel blocker, angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB) (James et al, 2014). Ponatinib treatment should be temporarily interrupted if HTN is not medically controlled (refer to Section 14.4.3 below for additional management recommendations). Patients may require urgent clinical intervention for HTN associated with confusion, headache, chest pain, or shortness of breath.

14.4 Management of Adverse Drug Reactions

Dose reduction guidelines are outlined in Sections 14.5 and 14.6. This section provides additional guidance for management of selected AEs for ponatinib.

Comprehensive assessments of any study drug-related AEs (adverse drug reactions) experienced by the patient will be performed throughout the course of the study. Anticipated adverse drug reactions that may be experienced are described in the Investigator's 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 trial.

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.

14.4.1 Vascular Occlusion

Serious arterial and venous thrombotic and occlusive adverse events, 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 occlusive adverse events were more frequent with increasing age and in patients with prior history of ischemia, hypertension, diabetes, or hyperlipidemia.

14.4.1.1 Arterial Occlusion and Thrombosis

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

Serious cerebrovascular adverse 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 adverse events were reported in ponatinib-treated patients. Cases of digital or distal extremity necrosis were reported in patients with diabetes mellitus and peripheral arterial disease; some of these required amputations.

Monitor and aggressively treat factors that increase cardiovascular risk, such as hypertension, cigarette smoking, hypercholesterolemia, and hyperglycemia. Interrupt and consider discontinuation of study drug in patients who develop arterial thrombotic adverse 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 and the patient has no other treatment options.

14.4.1.2 Venous Thromboembolism

Serious venous thromboembolic adverse 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 thromboembolic adverse events.

Ponatinib should not be restarted in patients with serious venous occlusive adverse events unless the potential benefit outweighs the risk of recurrent venous occlusions and the patient has no other treatment options.

14.4.2 Congestive Heart Failure and Left Ventricular Dysfunction

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

14.4.3 Hypertension

Blood pressure should be monitored at each visit. Hypertension (HTN) detected by at least 2 blood pressure measurements should be graded according to CTCAE version 4.0, which defines HTN as a disorder characterized by a pathological increase in blood pressure; a repeated elevation in the blood pressure exceeding 140 mm Hg for systolic over 90 mm Hg for diastolic. For patients who develop HTN or worsening HTN during study treatment, aggressive antihypertensive medication should be initiated or optimized to achieve target blood pressure before interruption or dose reduction of the study treatment at the discretion of the investigator. If hypertension is persistent despite adequate anti-hypertensive therapy including titration of anti-hypertensive medication or introduction of additional anti-hypertensive medications, or if grade 4 HTN develops, dose interruption and reduction is recommended according to Dose Modification Guidelines for general non-hematologic AEs in Table 14-1.

14.4.4 Cardiac Arrhythmias

Supraventricular tachyarrhythmias were reported in patients treated with ponatinib. Advise patients to report signs and symptoms of rapid heart rate (palpitations, dizziness). Symptomatic bradyarrhythmias have also been reported. Advise patients to report signs and symptoms suggestive of slow heart rate (fainting, dizziness, or chest pain, see Table 14-1).

14.4.5 QT Prolongation

The QT interval-prolonging potential of ponatinib was assessed in 39 leukemia patients, and no clinically significant QT prolongation was observed. This finding was confirmed in ECG observations of 140 patients in the ponatinib arm of the phase 3 trial. However, a thorough QT study has not been performed. Therefore, a clinically significant effect on QT cannot be excluded.

14.4.6 Hemorrhage

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

14.4.7 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.

14.4.8 Neuropathy

Serious peripheral and cranial neuropathic adverse events have occurred in ponatinib-treated patients. In clinical trials, serious peripheral neuropathic adverse events 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, discomfort, a burning sensation, neuropathic pain, or weakness. Consider interrupting ponatinib as described in Section 14.6 and evaluate any suspected neuropathy.

14.4.9 Ocular Toxicity

Serious ocular adverse event toxicities leading to blindness or blurred vision have occurred in ponatinib-treated patients. Retinal toxicities including macular edema, retinal vein occlusion, and retinal hemorrhage have also occurred in ponatinib-treated patients. Other ocular toxicities include cataracts, glaucoma, iritis, iridocyclitis, and ulcerative keratitis. Conduct comprehensive eye exams when clinically indicated. See Table 14-1 for details.

14.4.10 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 management of laboratory abnormalities should be managed with dose interruption and/or dose reduction according to Table 14-1.

14.4.11 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 both 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 on 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 14-1 for details.

14.4.12 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 Table 14-1.

14.4.13 Myelosuppression

Neutropenia, anemia, and thrombocytopenia have been observed in clinical studies of ponatinib in patients with CML. While myelosuppression can occur at any time during treatment, its onset in CML patients most commonly occurs within the first month on treatment. Myelosuppression can partially be attributed to the CML itself; however, treatment with ponatinib could also contribute. These events can typically be managed with supportive care and, if felt to be treatment-related, either a reduction or interruption of treatment with ponatinib 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, and granulocyte-macrophage colony-stimulating factor is permitted on study; these agents may be used to support blood counts as clinically indicated to minimize treatment interruptions or repeated dose reductions.

The important clinical AE of febrile neutropenia falls under the broad category of myelosuppression. If a patient's individual risk factors place them at high risk of developing febrile neutropenia, primary prophylactic use of colony-stimulating growth factors for the prevention or reduction of febrile neutropenia is recommended according to the published NCCN guidelines [NCCN Guidelines Version 1, 2012 – Myeloid Growth Factors].

14.4.14 Tumor Lysis Syndrome (TLS)

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

14.4.15 Rash and/or Pruritus

Skin rashes have been commonly reported to be associated with ponatinib. The vast majority of the 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 dermititis. Occasionally, patients treated with ponatinib have been reported to have a dry, flaky or exfoliative type of rash or a psoriasiform dermatitis. Rarely, an erythema multiforme type of rash has been associated with ponatinib.

Most patients can be maintained on the current dose of ponatinib, uninterrupted, and if necessary their symptoms can be managed with antihistamines, emollients, or topical steroids. If dose interruption is indicated, patients can resume the same dose of ponatinib typically without recurrence of symptoms once the original episode has improved or resolved. Interrupt administration in the case of serious or severe (grade 3 or 4) rash and follow the dose modification guidelines for non-hematologic toxicity in Table 14-1.

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

14.4.17 Constitutional Symptoms/Joint Pain

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

14.5 Dose Delays and Reductions

Dose delays and/or reductions will be implemented for patients who experience adverse drug reactions as indicated in the following sections.

14.6 Dose Delay and/or Reduction for Adverse Events (AEs) Attributable to the Study Drug

Table 14-1 describes guidelines for dose modification due to study-drug-related toxicity, graded according to NCI CTCAE v4.0. These guidelines should be followed by clinical investigators; however, for an individual patient, dose interruptions, reductions and treatment discontinuation should also be based on the clinical circumstance. Deviation from these guidelines should 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 and QTcF prolongation) 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 14-1. There are no suggested dose modifications for grade 1 or 2 hematologic toxicities.

Guidelines for assessment and management of pancreatitis and QTcF prolongation are described in Table 14-1 also.

Pancreatic toxicities may be 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: the recent update of NCI CTCAE version 4 has changed the grading of pancreatitis from the grading system in version 3. CTCAE version 4 in the Gastrointestinal disorder section defines grade 2 pancreatitis as "enzyme elevation or radiologic findings only." Version 4 separately defines toxicity grades for isolated elevation of lipase or serum amylase, found in the Investigations section of the guidance. Refer to Table 14-1 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 14-1. 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 14-1 Modifications for Adverse Events (AEs) Attributable to Study Drug

Non-hematologic Toxicity	
Grade 2 Persistent 7 days with optimal care	First occurrence at any dose level: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level Recurrence* at 45 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 30 mg Recurrence at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Recurrence at 15 mg: Discontinue ponatinib
Grade 3 or 4	Occurrence** at 45 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 30 mg Occurrence at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Occurrence at 15 mg: Discontinue ponatinib

Pancreatitis and Elevation of Lipase	
Asymptomatic grade 1 or 2 elevation of serum lipase	Consider interruption or dose reduction of ponatinib
Asymptomatic grade 3 or 4 elevation of lipase (> 2 × ULN) or asymptomatic radiologic pancreatitis (grade 2 pancreatitis)	Occurrence at 45 mg: Hold until event is ≤ grade 1 (≤ 1.5 x ULN), or has returned to baseline Resume at 30 mg Occurrence at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Occurrence at 15 mg: Discontinue ponatinib
Symptomatic grade 3 pancreatitis (severe pain, vomiting, medical intervention indicated [eg, analgesia, nutritional support])	Occurrence at 45 mg: Hold until complete resolution of symptoms and lipase elevation is ≤ grade 1, or has returned to baseline Resume at 30 mg Occurrence at 30 mg: Hold until complete resolution of symptoms and lipase elevation is ≤ grade 1, or has returned to baseline Resume at 15 mg Occurrence at 15 mg: Discontinue ponatinib
Grade 4 pancreatitis	Discontinue ponatinib
Hepatic Toxicity	
Elevation of liver transaminase > 3 × ULN (grade 2 or higher)	Occurrence at 45 mg: Hold and monitor hepatic function until event is ≤ grade 1 (≤3 × ULN), or has returned to baseline Resume at 30 mg Occurrence at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Occurrence at 15 mg: Discontinue ponatinib
Elevation of AST or ALT ≥ 3 × ULN concurrent with an elevation of bilirubin > 2 × ULN and alkaline phosphatase < 2 × ULN	Discontinue ponatinib

LVEF/CHF[1]	
Grade 2	First occurrence at any dose level: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level Recurrence* at 45 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 30 mg Recurrence at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Recurrence at 15 mg: Discontinue ponatinib
Grade 3	Occurrence** at 45 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 30 mg Occurrence at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Occurrence at 15 mg: Discontinue ponatinib
Grade 4	Discontinue ponatinib.

Skin Rash	
Grade 2 persistent despite optimal symptomatic therapy	First occurrence at any dose level: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level Recurrence at 45 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 30 mg Recurrence at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Recurrence at 15 mg: Discontinue ponatinib
Grade 3 persistent despite optimal symptomatic therapy	First occurrence at any dose level: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level Recurrence at 45 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 30 mg Recurrence at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Recurrence at 15 mg: Discontinue ponatinib

Prolonged QTcF	
Grade 2 (QTcF 481-500 ms)	First occurrence at any dose level: Hold ponatinib Perform serum electrolyte analysis (including potassium, calcium and magnesium) and correct with supplements if below normal limits Review concomitant medications Repeat ECG as clinically indicated, but at least daily until QTcF returns to ≤ grade 1 (480 ms) Resume at 45 mg after recovery to ≤ grade 1 If no contributing reason was identified for QTcF elevation then weekly ECG monitoring is recommended for 4 weeks upon resumption of ponatinib, then monthly for 6 months, and then every 3 months for the remainder of the study, or more frequently as clinically indicated Recurrence at 45 mg: Repeat above Resume at 30 mg after recovery to ≤ grade 1, or until event has returned to baseline Recurrence at 30 mg: Repeat above Resume at 15 mg after recovery to ≤ grade 1, or until event has returned to baseline Recurrence at 15 mg: Discontinue ponatinib
Grade 3 (QTcF ≥ 501 ms on at least 2 separate ECGs)	First occurrence at any dose level: Hold ponatinib Perform serum electrolyte analysis (including potassium, calcium and magnesium) and correct with supplements if below normal limits Review concomitant medications Repeat ECG as clinically indicated, but at least daily until QTcF returns to ≤ grade 1 (480 ms) Resume at 30 mg after recovery to ≤ grade 1 If no contributing reason was identified for QTcF elevation then weekly ECG monitoring is recommended for 4 weeks upon resumption of ponatinib, then monthly for 6 months, and then every 3 months for the remainder of the study, or more frequently as clinically indicated Recurrence at 45 mg: Repeat above Resume at 30 mg after recovery to ≤ grade 1, or until event has returned to baseline Recurrence at 30 mg: Repeat above Resume at 15 mg after recovery to ≤ grade 1, or until event has returned to baseline Recurrence at 15 mg: Discontinue ponatinib
Grade 4	Discontinue ponatinib Consult Sponsor

Hematologic	
ANC/platelets	
Grade 3 or 4	First occurrence at any dose level: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level Recurrence at 45 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 30 mg Recurrence at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Recurrence at 15 mg: Discontinue ponatinib

* "Recurrence" means the second time an AE is encountered by a patient at a given dose level.
** "Occurrence" means the first time an AE is encountered by a patient at a given dose level.
Definitions: ANC = absolute neutrophil count; CHF = congestive heart failure; CT = computed tomography; LVEF = left ventricular ejection fraction.
[1]Note: CTCAE criteria should be used to interrupt or discontinue study drug for grade 2, 3, or 4 events considered to be study drug related.
For grade 2: LVEF < 50% - 40%, grade 3: LVEF < 39 - 20%, grade 4: refractory CHF or LVEF < 20%.

14.6.1 Dose Modifications for Vascular Occlusive Events

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

Vascular occlusive events include a broad range of non-specific terms that could meet the criteria for diagnosis of a vascular occlusive event. Investigators should use their clinical judgment and medical knowledge of the specific terms in describing these vascular occlusive events.

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

14.6.1.1 Arterial Thrombotic and Occlusive Events

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

Patients should be discontinued from ponatinib in the event of myocardial infarction (MI), unstable angina, cerebrovascular accident or transient ischemic attack (TIA), or revascularization procedures, unless for that individual patient, the investigator believes the potential benefits of ponatinib treatment exceed the risks of continued treatment.

For all other arterial thrombotic occlusive events, the dose modification guidelines are outlined in Table 14-2.

Table 14-2 Dose Modifications for Arterial Thrombotic Occlusive Events

Vascular Occlusion: Other Cardiovascular and Cerebrovascular Events	
Grade 1	Consider interruption or dose reduction of ponatinib until the event resolves.
Grade 2	First occurrence** at any dose level: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level. Recurrence* at 45 mg: Discontinue study drug Recurrence at 30 mg: Discontinue study drug Recurrence at 15 mg: Discontinue study drug
Grade 3 and 4	Discontinue ponatinib.
Other Vascular Occlusions including Peripheral Vascular Events	
Grade 1	Consider interruption or dose reduction of ponatinib until the event resolves.
Grade 2	First occurrence at any dose level: Hold until event is ≤ grade 1, or has returned to baseline Resume at current dose level Recurrence at 45 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 30 mg Recurrence at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Recurrence at 15 mg: Discontinue ponatinib
Grade 3	Occurrence at 45 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 30 mg Occurrence at 30 mg: Hold until event is ≤ grade 1, or has returned to baseline Resume at 15 mg Occurrence at 15 mg: Discontinue ponatinib
Grade 4	Discontinue ponatinib.

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

14.6.1.2 Venous Thromboembolic Events

Patients should be discontinued from study drug in the event of life-threatening pulmonary embolism and retinal vein thrombosis.

For all other venous thromboembolic events, the dose modification guidelines are outlined in Table 14-3.

Table 14-3 Dose Modifications for Venous Thromboembolic Events

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

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

14.7 Dose Re-Escalation after Resolution of Adverse Drug Reactions

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

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

Patients may receive step-wise dose escalations if the above criteria continue to be met (eg, 15 mg daily to 30 mg daily to 45 mg daily) up to the limitations outlined in Section 13.4.

Note: patients with grade ≥3 LV dysfunction, CHF, or vascular occlusion events are not eligible for dose re-escalation after resolution of their symptoms.

14.8 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). Tablets will be supplied as follows:

45 mg tablets: 30 count in 30 cc white high density polyethylene (HDPE) bottles with induction-sealed child resistant caps.

15 mg tablets: 60 count in 30 cc white HDPE bottles with induction-sealed child resistant caps. Note: 15 mg tablets will be used for patients reducing dose.

Bottle labels will bear the appropriate label text as required by governing regulatory agencies. At a minimum, such text will include product name, product strength, number of tablets, and lot number.

14.9 Storage and Stability

The recommended storage condition for ponatinib is room temperature.

14.10 Study Drug Accountability

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 (45 mg or 15 mg), the number of tablets dispensed with the corresponding lot number, and the initials of the person dispensing the drug. These logs are to be maintained by the study pharmacist in the pharmacy throughout the duration of the study and will be periodically verified by a representative of the Sponsor. The Investigator is responsible for ensuring that the patient diary card(s) and study drug provided to the patient and returned from the patient are accounted for and noted in source documentation.

14.11 Disposition of Used Supplies

All used bottles of study drug must be destroyed in an appropriate manner according to the standard practice at each study center. Destruction of such supplies will be documented, and a representative of the Sponsor will verify disposition records.

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

No other utilization of ponatinib intended for use in this study is authorized by the Sponsor. The Principal Investigator or his/her designee will be responsible for the appropriate handling and disposition of residual study drug. Each site is responsible for proper and careful destruction of study drug returned by patients.

14.12 Inventory of Unused Supplies

Periodically, throughout and at the conclusion of the study, a representative of the Sponsor will conduct an inventory of unused study drug. At the completion of the trial, a final study drug accountability review will be conducted. Any discrepancies must be investigated and all unused study drug must be destroyed on site per the standard operating procedures of the investigative site.

15 CONCOMITANT TREATMENT

All concomitant medications administered from the time of informed consent signature through the 30-day Follow-up Visit are to be reported on the appropriate eCRF for each patient.

Prior Treatment

Reasonable efforts will be made to collect information on all prior cancer treatments received by the patient (chemotherapy, radiotherapy, immunotherapy, biologics, etc.). The information must be obtained from the patient's medical chart and recorded on the patient's eCRF.

15.1 Permitted Treatment

All routine and appropriate supportive care (including blood products) will be allowed during this study, as clinically indicated, and in accordance with the 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 or erythropoietin for limited times.
- Where appropriate, hydroxyurea or anagrelide are 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, and is thereafter prohibited.

15.2 Prohibited Treatment

The following concurrent medications and treatments are prohibited:

- Any other anticancer therapy including, but not limited to, chemotherapeutic agents, immunotherapy, biological response modifiers, radiotherapy, surgery and/or systemic hormonal therapy (hematopoietic growth factors are permitted). 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 (see exclusion criteria 9).
- Use of any other investigational drug or device.
- Use of medications with a known risk of Torsades de Pointes (see Attachment B).

- Herbal preparations or related over-the-counter preparations containing herbal ingredients (eg, St. John's Wort, Blue Cohosh, Estroven) either during or within 2 weeks prior to the first dose of ponatinib.
- Elective surgery requiring in-patient care.

Medications that are potent inhibitors or inducers of CYP3A4 (see Attachment C) should be avoided, but are not prohibited (see Section 15.3).

Medications that prolong the QT interval should be avoided, but are not prohibited. If such medications are necessary, and used while a patient is on study, then additional ECG monitoring should be performed as clinically indicated.

15.3 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 trials using the recommended daily dose of 45 mg. In vitro studies also demonstrate that human CYP3A4 is involved in the metabolism of ponatinib. In view of this, a drug interaction study was performed with a strong CYP3A4 inhibitor in healthy subjects. Ketoconazole co-administration increased ponatinib C_{max} and AUC by 47% and 78%, respectively. Since CYP3A4 contributes to the metabolism of ponatinib, strong inducers or inhibitors of CYP3A4 should be used with caution or avoided altogether. If co-administration with strong inhibitors of CYP3A4 is unavoidable, consider reduction of the ponatinib dose 1 level from the current (that is, 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 CYP3A4 inhibitor or, if that is not possible, consult the sponsor.

Medicines that are associated with the prolongation of the QT interval may interact with ponatinib as well and contribute to QT interval prolongation, which has the potential to contribute to ventricular arrhythmia. In addition, some medicines associated with QT prolongation also interact with the CYP3A4 cytochrome and an effect on the QT interval might thus be exacerbated. Concomitant administration of medicines with a known risk of Torsades de Pointes are prohibited (see Attachment B). Medicines that otherwise prolong the QT interval should be avoided.

Concomitant use of ponatinib with anti-platelet agents and anticoagulants should be approached with caution in patients who may be at risk of bleeding events (see Section 14.4.6 Hemorrhage and Section 14.4.13 Myelosuppression).

16 MEASURES TO MINIMIZE/AVOID BIAS

16.1 Patient Registration and Identification

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

17 SAFETY

17.1 Safety Variables

Safety will be assessed by physical examination, interim history, and laboratory assessments. Adverse events will be graded according to the NCI CTCAE, v. 4.0 (see Study Reference Manual).

17.2 Safety Assessment Methods

Safety will be assessed by physical examination, interim history, and laboratory assessments. Adverse events will be graded according to the NCI CTCAE, v. 4.0 (see Study Reference Manual).

17.3 Safety Laboratory Assessments

The local laboratory of the institution where the trial is being conducted will be used to process the laboratory samples. Clinically significant laboratory abnormalities (eg, those that lead to some sort of intervention) are to be assessed as AEs and recorded on the appropriate eCRF.

18 EFFICACY

18.1 Efficacy Variables

Primary efficacy endpoints are listed in Section 11.2. The primary endpoints are:

1. For CML patients in CP at study entry: MCyR, defined as CCyR or PCyR.

   CP patients in CCyR are **not** eligible for this study; as such, they would not be eligible for inclusion in the efficacy analysis.

2. For CML patients in AP at study entry: MaHR, defined as CHR or no NEL.

   AP patients in MaHR are **not** eligible for this study; as such, they would not be eligible for inclusion in the efficacy analysis.

3. For CML patients in BP at study entry or Ph+ ALL patients: MaHR, consisting of CHR or NEL.

   BP and Ph+ ALL patients in MaHR are **not** eligible for this study; as such, they would not be eligible for inclusion in the efficacy analysis.

Secondary endpoints for efficacy are defined in Section 11.2. They are:

1. For CML patients in CP:
   a. Hematologic responses: CHR;
   b. Cytogenetic responses: confirmed MCyR; and
   c. Molecular responses: MMR.
2. For CML patients in AP or BP or Ph+ ALL patients:

a. Cytogenetic responses: CCyR, PCyR, confirmed MCyR; and

a. Molecular responses: MMR.

3. For all patients: time to response, duration of response, progression free survival, and overall survival.

4. For all patients: safety and tolerability.

The exploratory endpoints of the study are:

1. For all patients: BCR-ABL sequence collection and analysis
2. For all patients: ASO PCR for T315I
3. For all patients: molecular genetic analyses.

Criteria that define the responses that constitute primary and secondary endpoints are included in Attachment A. In addition, criteria to define progression are also listed in Attachment A.

18.2 Efficacy Assessment Methods

Cytogenetic response will be assessed on BM biopsies and aspirations using standard methods for quantifying the proportion of Ph+ chromosomes. 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, 2012) clinical practice guidelines (accessed 21 March 2014). Conventional banding must be utilized, preferably on at least 20 metaphase cells. If BM sampling is insufficient and less than 20 metaphases are evaluable, the absolute result should be reported and the percentage calculated. Bone marrow samples will be obtained according to the Schedule of Events, Section 8. A BM sample may be obtained more frequently if clinically indicated.

The primary endpoint will be based on an unconfirmed MCyR. That is, the detection of a complete or partial cytogenetic response on a single BM aspirate will qualify as a response for the determination of efficacy. Confirmed MCyR is a secondary endpoint. In addition, duration of response will be measured as described in the statistical analysis plan.

Hematologic responses will be assessed on peripheral blood samples using standard methods to obtain a CBC with differential. Peripheral blood samples will be obtained according to the Schedule of Events, Section 8.

Complete hematologic response in CP will be confirmed. That is, the detection of CHR on a CBC at a single time point will require confirmation by CBC at least 4 weeks later to qualify as a response. A concurrent BM aspirate need not be done to assess CHR in CP patients.

Major hematologic response will be confirmed in patients in AP, BP, or with Ph+ ALL. That is, the detection of a CHR or NEL at a single time point will require confirmation at least 4 weeks later with a peripheral blood CBC and differential to qualify as a response for the determination of the primary endpoint for efficacy. The BM aspirate need not be repeated for confirmation.

19 STATISTICAL ANALYSIS

19.1 Sample Size and Power

19.1.1 Overview of Trial Design

This is a phase 2, single-arm trial in patients with CML and Ph+ ALL.

Table 19-1 summarizes the number of patients planned to be recruited in each cohort:

Table 19-1 Planned Number of Patients for Each Cohort

	Chronic Phase (CP)	Accelerated Phase (AP)	Blast Phase (BP)/Leukemia	Total
Resistant/intolerant to dasatinib or nilotinib	100 (Cohort A)	40 (Cohort C)	40 (Cohort E)	180
T315I mutation	60 (Cohort B)	40 (Cohort D)	40 (Cohort F)	140
Total	160	80	80	320

Cohort A will consist of CP CML patients resistant or intolerant to dastinib or nilotinib. Cohort B will consist of CP CML patients with T315I mutations. Cohorts C and E will consist of AP and BP/Ph+ ALL respectively, who are resistant or intolerant dasatinib or nilotinib. Cohorts D and F will consist of AP and BP/Ph+ ALL patients, respectively, with the T315I mutation.

Each of the 6 cohorts proposed in this trial are representative of distinct patient populations with different primary endpoints. Each cohort of patients will be analyzed separately for efficacy. The safety data from all cohorts will be pooled for the purpose of describing the safety of all treated patients as a whole. These cohorts can be viewed as 6 separate studies that are enrolled through a single "umbrella" protocol; therefore, no adjustments for multiplicity are planned.

19.1.2 Sample Size Determination: Cohorts A and B

The primary endpoint for this trial for patients with chronic CML (Cohorts A and B) will be MCyR. The MCyR rate is defined as the proportion of patients who have achieved a CCyR or PCyR after the initiation of study treatment.

The primary analysis of the primary endpoint of MCyR will be performed using a 2-sided exact 95% confidence interval (CI) for MCyR rate among all treated patients in each cohort.

Data on the use of second generation TKIs in patients who have failed dasatinib and nilotinib are available in several small studies (Giles et al, 2007; Quintas-Cardama et al, 2007; Garg et al, 2009). These 3 studies demonstrate an approximately 30% MCyR in these patients. However, these are highly selected patient populations; they do not include patients who have failed more than 2 agents, and responses are typically of short duration. Thus, for the purposes of this trial, the null or uninteresting MCyR rate is set at 20% for Cohort A (resistant and intolerant CP

patients). The alternative MCyR rate is set at 35% for Cohort A. The overall alpha level for each cohort will be set at 0.05. With a cohort size of 100 patients, a minimum of 29 responders (ie, those with a CCyR and a PCyR) would need to be observed in Cohort A in order to observe an exact 95% CI such that the lower bound exceeds 20% and the upper bound exceeds 35%. Therefore, 100 patients will provide at least 85% power to distinguish between a null response rate of 20% and an alternative response rate of 35% in Cohort A. The study will also provide at least 98% power to distinguish between 20% and 40%, in which case 29 responses will also be required, and at least 78% power to distinguish between 30% and 45%, in which case 40 responses would be required.

With a cohort size of 100 patients, the maximum width of the exact 95% CI will be approximately 20% when the MCyR rate is in the expected range of 20% to 35%.

For Cohort B (T315I CP patients), the null or uninteresting MCyR rate is set at 10% and the alternative MCyR rate is set at 35%. Data on the use of second generation drugs (Muller et al, 2009; Garg et al, 2009) in these patients suggest that less than 10% of patients achieve MCyR. With a cohort size of 60 patients, a minimum of 14 responders would need to be observed in Cohort B in order to observe an exact 95% CI such that the lower bound exceeds 10% and the upper bound exceeds 35%. Therefore, 60 patients will provide approximately 98% power to distinguish between a null response rate of 10% and an alternative response rate of 35% in Cohort B.

With a cohort size of 60 patients, the maximum width of the exact 95% CI will be 25% when the MCyR rate is in the expected range of 10% to 35%.

19.1.3 Sample Size Determination: Cohorts C-F

The sample sizes for Cohorts C to F (AP, and BP/Ph+ ALL) are based on similar considerations for each cohort (Garg et al, 2009). The endpoint for these cohorts is the MaHR. The MaHR rate is defined as the proportion of patients achieving a CHR or NEL response. The null or uninteresting MaHR rate is set at 10% and the alternative MaHR 30%. With a cohort size of 40 patients, a minimum of 9 responders would need to be observed in cohorts C to F in order to observe an exact 95% CI such that the lower bound exceeds 10% and the upper bound exceeds 30%. Forty patients in each cohort will provide approximately 89% power to distinguish between the null response rate of 10% and an alternative response rate of 30% in these cohorts.

19.1.4 Overall Sample Size

As described in preceding Sections 12.5 and 19.1.1, for each disease phase, after the initiation of treatment, patients will be tested for the T315I mutation. Depending on the outcome of the test, patients will be assigned to a resistant/intolerant cohort (cohorts A, C or E, respectively, depending on disease phase) or a T315I cohort (cohorts B, D, or F). For example, a CP patient will be tested and assigned to cohort A or B, an AP patient will be assigned to cohorts C or D, and a BP or Ph+ ALL patient will be assigned to cohort E or F. Therefore, enrollment and assignment to the paired cohorts comprising a disease phase are linked by the relative prevalence of T315I patients and the T315I testing scheme.

Early enrollment experience demonstrates that patients whose disease is resistant or intolerant to therapy are relatively more common than patients who carry the T315I mutation.

Thus, the mutation testing schema will lead to a relative over-availability of resistant and intolerant patients compared with T315I patients. Therefore, cohorts A, C, and E may fill before the T315I cohorts B, D and F will reach their target sample sizes. Since the scientific objectives of the study require meeting the target accrual goals for the T315I cohorts (and, indeed, all cohorts), it is anticipated that the higher relative proportion of resistant/intolerant patients to T315I patients will require over-enrollment of the resistant/intolerant cohorts (A,C, and E) to ensure full T315I patient enrollment.

Thus, overall enrollment will be determined by the need to fill the T315I cohorts. At the time of this amendment, it is anticipated the trial may require up to 450 patients to ensure reaching the planned sample sizes of the T315I cohorts. Individual cohorts may be closed by the Sponsor to control overall enrollment to the study.

19.2 Statistical and Analytical Plans

19.2.1 Analysis Populations

Treated Population:

Cohorts A and B

This population includes all patients assigned to Cohort A or B who have received at least 1 dose of study drug. Patients for whom the T315I sample is not received before the first assessment of the primary outcome who are resistant to either dasatinib or nilotinib will be assigned to Cohort A. Patients who are not confirmed to have a detectable T315I mutation by direct sequencing before the first cytogenetic assessment and are not resistant to dasatinib or nilotinib will not be included in the treated population and will be analyzed separately (refer to Section 12.5). We estimate that approximately 10% of patients with a history of a T315I mutation will not be resistant or intolerant to dasatinib or nilotinib and lack the mutation by direct sequencing. We also estimate that this situation will most likely apply to the CP candidates, as patients with AP, BP and Ph+ ALL will most likely have received more extensive therapy. Thus, we estimate that fewer than 10 patients will fall into this group.

Cohorts C-F

This population includes all patients assigned to one of Cohort C-F who have received at least 1 dose of study drug. Patients in AP CML for whom the T315I sample is not received before the BM aspirate, and who are resistant to either dasatinib or nilotinib will be assigned to Cohort C. Patients in BP CML and Ph+ ALL patients for whom the T315I sample is not received before the first BM aspirate, and who are resistant to either dasatinib or nilotinib will be assigned to Cohort E. Patients who are not confirmed to have a detectable T315I mutation by direct sequencing before the first BM aspirate and are not resistant to dasatinib or nilotinib will not be included in the treated population and will be analyzed separately (refer to Section 12.5). It is estimated that approximately 10% of patients with a history of a T315I mutation will not be resistant or intolerant to dasatinib or nilotinib and lack the mutation by direct sequencing. It also is estimated that this situation will most likely apply to the CP candidates, as patients with AP, BP and Ph+ ALL will most likely have received more extensive therapy. Thus, fewer than 10 patients are expected to fall into this group.

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

19.2.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized separately for each cohort and will include at a minimum: age, gender, race, weight, country/region, and disease characteristics (eg, time since diagnosis, duration of chronic disease, mutation status).

19.2.3 Efficacy Analyses

All efficacy analyses will be performed separately by each cohort (designated A through F) and will include all patients in the treated population.

19.2.3.1 Definitions of Efficacy Endpoints

Primary efficacy endpoints for this trial are defined as follows:

- Major cytogenetic response (MCyR), which is defined as CCyR or PCyR. Patients entering the trial already in PCyR must achieve a CCyR in order to be considered as achieving a MCyR. The criteria for response are given in Attachment A.
- Major hematologic response (MaHR), which is defined as CHR and NEL. Major hematologic response will be confirmed by a peripheral blood CBC and differential no earlier than 28 days later. The criteria for response are given in Attachment A.

Secondary efficacy endpoints for this trial 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 trial in PCyR, confirmed MCyR will be defined as 2 assessments of CCyR at least 28 days apart.
- Major Molecular Response (MMR) (as defined in Attachment 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 Attachment A) are met, censored at the last date at which the criteria for response are met. An additional analysis will be performed defining the duration as the time from the first assessment at which the criteria for response are met until the last assessment 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 in Attachment 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 trial are defined as follows:

- BCR-ABL sequence analysis will be collected and compared with response to therapy.

- ASO PCR for T315I will be collected and compared with T315I status by history and by direct sequencing during screening, as well as with response to therapy.
- Molecular genetic analyses will be performed to better understand outcomes.

19.2.3.2 Primary Endpoint Analysis

Cohorts A and B

The primary analysis of the primary endpoint of MCyR will be performed using a 2-sided exact 95% CI for the MCyR rate and will be based on the total patients enrolled in each cohort. Major cytogenetic response rate is defined as the proportion of patients who have achieved a CCyR or PCyR after the initiation of study treatment. Patients entering the trial already in PCyR must achieve a CCyR in order to be considered a success for the MCyR rate.

Cohorts C-F

Major hematologic response rate is defined as the proportion of patients who have achieved a confirmed CHR or NEL after the initiation of study treatment. The primary analysis of the primary endpoint of MaHR will be performed using a 2-sided exact 95% CI for MaHR rate and will be based on the total patients enrolled in each cohort.

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

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

- All CP CML patients (Cohorts A and B) who do not respond by 12 months after the initiation of study treatment will be analyzed as non-successes.
- All AP/BP phase CML patients and Ph+ ALL patients (Cohorts C, D, E and F) who do not respond by 6 months after the initiation of study treatment will be analyzed as non-successes.
- Patients who are not confirmed to have a positive T315I mutation testing result by the first cytogenetic assessment (CML patients in CP) or BM aspirate (CML patients in AP or BP and Ph+ ALL patients) and are resistant or intolerant to either dasatinib or nilotinib will be assigned to cohort A, C, or F (resistant/intolerant cohorts).
- 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 Attachment A) are not available, the patient will be considered as not a success for that particular visit.

19.2.3.3 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 trial 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 2-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 95% CI will be calculated. An additional analysis will be performed defining the duration as the time from the first assessment at which the criteria for response are met until the last assessment at which the criteria for response are met.
- Progression-free survival and overall survival, and time to response will be estimated using the Kaplan-Meier method. The median duration of response and 95% CI will be calculated.

1.1.1.1.1 Data Handling Rules for Secondary Endpoint Analyses

In addition to the data handling rules specified in Section 19.2.3.2.1, the following key data handling rules for the secondary efficacy analyses will be implemented (note that the definition of progression is specified in Attachment A):

- Loss of MCyR is defined as meeting any of the following criteria:
  - In patients entering the trial in PCyR: 2 consecutive cytogenetic assessments ≥ 28 days apart with Ph+ > 0%. Patients with a single cytogenetic assessment with Ph+ > 0% followed by no additional cytogenetic assessments will be also considered as meeting the criteria for loss of MCyR.
  - In patients entering the trial not in PCyR: 2 consecutive cytogenetic assessments 28 days apart with Ph+ > 35%. Patients with a single cytogenetic assessment with Ph+ > 35% followed by no additional cytogenetic assessments will be also considered as meeting the criteria for loss of MCyR.
- Loss of MaHR (Cohorts C through F) is defined as 2 consecutive hematologic assessments ≥ 4 weeks apart at which at the criteria for MaHR are not met. Patients with a single hematologic assessment at which the criteria for MaHR are not met followed by no additional hematologic assessments will be also considered as meeting the criteria for loss of MaHR.
- Patients who progress after a single missed or incomplete visit will be considered as having progressed at that visit.
- Patients who progress after 2 or more missed or incomplete visits will be censored at the last visit at which the response criteria are met.

19.2.4 Safety Analyses

All patients receiving at least 1 dose of study drug will be considered evaluable for safety. The AE incidence rates as well as the frequency of occurrence of overall toxicity, categorized by toxicity grades (severity) will be described for each cohort of the trial. Listings of laboratory test results will also be generated, and descriptive statistics summarizing the changes in laboratory tests over time will be presented.

19.3 Procedures for Reporting Deviations to Original Statistical Analysis Plan

All deviations from the original statistical analysis plan will be provided in the final clinical study report.

20 STEERING COMMITTEES

Two steering committees will be constituted prior to the initiation of the trial. Their purpose will be to function in an advisory capacity to: 1) provide input on the conduct of the trial; 2) insure scientific and ethical integrity of the trial during its course; and 3) provide ongoing oversight of the safety and efficacy components of this open-label study.

The steering committees will be composed of expert clinicians. There will be 2 committees. The clinical committee will be composed of clinicians most expert in the clinical care and investigation of the included patient populations. It will be responsible for general trial oversight. The molecular committee will be charged with oversight of the molecular components of the trial, including mutation detection methods, molecular monitoring strategies and techniques, and other correlative studies. The Sponsor will take part in both clinical and molecular steering committee meetings.

The steering committees will review data at intervals during the trial to evaluate the safety profile of the drug, to assess accumulating signals of efficacy, evaluate data quality, and to provide input on operational aspects of the study. They may make recommendations for the Sponsor's consideration based on periodic review.

21 CONTRAINDICATIONS, PRECAUTIONS AND WARNINGS

21.1 Precautions Regarding Conception, Pregnancy, and Nursing

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.

Female and male patients 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 ponatinib, and again at treatment discontinuation. A negative pregnancy test must be documented prior to administration of the study drug.

If a patient is confirmed to be pregnant during the trial, study drug administration must be discontinued immediately. Any pregnancy occurring during this study is to be reported as a serious adverse event (SAE). The Investigator must immediately notify the medical monitor about the pregnancy and record it as an SAE on the SAE Form as well as on the AE page of the eCRF (or other eCRF specifically provided for this purpose). In addition, the Investigator must 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, unless the patient has received other anticancer therapy.

Once the newborn is determined to be healthy, as defined by and agreed upon by the Investigator(s) and the Sponsor, additional follow-up will no longer be required.

21.2 Overdose

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

22 ADVERSE EVENTS

22.1 Adverse Event (AE) Definition

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have 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 the medicinal product. Any worsening of a preexisting condition, which is temporally associated with the use of the study drug, is also an AE.

Adverse events include:

- Suspected adverse drug reactions;
- Reactions from study drug overdose, abuse, withdrawal, sensitivity, or toxicity;
- Significant changes or abnormalities when compared to baseline, in signs, symptoms, clinical laboratory results, or physiological testing. This includes any worsening of a pre-existing condition temporally associated with the use of study drug;
- Other untoward medical events, regardless of their relationship to the study drug, such as injury, events that require surgery, accidents, extensions of symptoms, or apparently unrelated illnesses.

Progression of disease is not considered an AE unless it results in hospitalization or death.

22.2 Evaluation of Adverse Events (AEs)

22.2.1 Determination of Seriousness

The Investigator will determine the seriousness of an AE based on the following.

22.2.1.1 Serious Adverse Event (SAE)

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

- Death: An AE that results in death during the active study period or within 30 days following Study Drug administration.
- Life-threatening adverse event: An AE that places the patient, in the view of the Investigator, at immediate risk of death from the event as it occurred (ie, this does not include a reaction that had it occurred in a more severe form, might have caused death).
- Permanent, persistent, or significant disability: A disability 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. Hospitalization for an elective or diagnostic procedure, or surgery for a pre-existing condition that has not worsened, is not considered and SAE.
- A congenital anomaly/birth defect: A fixed, permanent impairment established at or before birth.
- Cancer: Occurrence or diagnosis of a new cancer during the trial is considered a serious event. A new cancer is one that is histopathologically different than the cancer under study in the trial (ie, metastatic or progressive disease would not be considered an SAE).
- Important medical event: Events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they jeopardize the patient and require medical or surgical intervention to prevent a life-threatening situation, hospitalization or death.

22.2.1.2 Adverse Events of Special Interest (AESIs)

Vascular occlusive events have been identified as AESIs for ponatinib. These include arterial and venous thrombotic and occlusive adverse events that meet the criteria for SAEs, defined above in Section 22.2.1.1, and those adverse events that do not meet the SAE criteria.

AESIs require ongoing monitoring by Investigators and rapid identification and communication by the Investigator to the sponsor. All AESIs, whether SAEs or not, must be reported immediately (within 24 hours) to the sponsor. The sponsor has determined that the events listed below (whether considered serious or non-serious by Investigators) should be considered AESIs and therefore should be reported within 24 hours (see Section 22.6).

A. Myocardial infarction: The Third Universal Definition of Myocardial Infarction (Thygesen et al, 2012) is used to define MI (see below)

B. Angina (newly diagnosed or worsening of existing angina or unstable angina)

C. Coronary artery disease (CAD) (newly diagnosed or worsening of existing CAD) or symptoms that may reflect cardiovascular disease (Thygesen et al, 2012)

D. Cerebrovascular ischemic disease including ischemic or hemorrhagic stroke, vascular stenosis, transient ischemic accident (TIA), cerebrovascular occlusive disease documented on diagnostic neuroimaging, or symptoms that may reflect cerebrovascular disease (Easton et al, 2009)

E. New onset or worsening of peripheral artery occlusive disease (eg, renal artery, mesenteric artery, femoral artery) or symptoms that may reflect peripheral vascular disease

F. Retinal vascular thrombosis, either venous or arterial

G. Venous thromboembolism, or symptoms that may reflect venous thrombosis, that could result in significant compromise of organ function or other significant consequences (eg, pulmonary embolism, portal vein thrombosis, renal vein thrombosis)

22.2.1.2.1 AESIs That May be Non-Serious

Signs/symptoms of vascular occlusive disease that are not fatal or life-threatening, do not require hospitalization or prolong hospitalization, and do not meet the definition above of SAEs, but ***that require medical evaluation***, are also considered AESIs and must be reported to the sponsor or the designated representative by completing the SAE/AESI form within 24 hours of awareness.

22.3 Determination of Severity

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

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

22.4 Determination of Relatedness

The Investigator will use medical consideration to determine the relatedness of an AE with the study drug based on the following definitions. Not all criteria in each category of relatedness must be present.

Definitely Not Related (not drug related)

- The patient did not receive study drug,

OR

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

OR

- There is another obvious cause of the AE.

Probably Not Related (not drug related)

- There is evidence of exposure to study drug.
- There is another more likely cause of the AE.
- Dechallenge (if performed) is negative or ambiguous.
- Rechallenge (if performed) is negative for ambiguous.

Possibly Related (drug related)

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

Probably Related (drug related)

- There is evidence of exposure to study drug.
- The temporal sequence of the AE onset relative to administration of the study drug is reasonable.
- The AE is more likely explained by the study drug than by another cause.
- Dechallenge (if performed) is positive.

Definitely Related (drug related)

- There is evidence of exposure to study drug.
- The temporal sequence of the AE onset relative to administration of the study drug is reasonable.
- The AE is more likely explained by the study drug than by another cause.

- Dechallenge is positive.
- Rechallenge (if feasible) is positive
- The AE shows a pattern consistent with previous knowledge of the study drug or study drug class

22.5 Documenting AEs

All AEs (including SAEs) are to be accurately recorded on the Adverse Event page of the patient's eCRF from the time the patient signs the informed consent until 30 days following the last study drug administration or withdrawal from study participation. Each event will be graded for severity, intensity, and relatedness (See "Evaluating Adverse Events"). The date of onset, as well as the duration of the event will be recorded. In addition, the method used to treat the AE and the outcome of the AE will also be noted.

AEs ongoing after the reporting period: Any ongoing AEs thought to be at least possibly study drug-related, and all ongoing SAEs and AESIs after this time should be followed at least every 4 weeks until they resolve to baseline (or CTCAE grade ≤1), stabilize, or are considered to be chronic/irreversible.

22.6 Reporting SAEs, AESIs, and Patient Deaths

Time Frame for Reporting

The following must be reported to the Sponsor or Sponsor's designee within 24 hours of becoming aware of the event:

Any death, SAE, or AESI experienced by the patient during the on-study period (ie, from the signing of informed consent to 30 days after the last dose of study drug).

Any death, SAE, or AESI that the Investigator becomes aware of, and believes to be study drug related, that occurs more than 30 days after the patient last received study drug.

Information to be Provided by the Investigator

Within 24 hours of learning about the SAE, AESI, or patient death, the Investigator must notify the Sponsor or designee and transmit information to the Sponsor or designee. Information should be provided on an SAE 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 AE,

- Relationship of the AE to the study drug,
- Outcome of the AE.

22.7 Follow-up Information

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 Principal Investigator.

Follow-up data concerning the SAE or AESI (eg, diagnostic test reports, physician's summaries, etc.) must be promptly reported (within 24 hours of receipt) to the Sponsor or Sponsor's designee, until resolution of the SAE or AESI. 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.

Required Follow-up for SAEs or AESIs

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 or AESIs. If an SAE or AESI continues after the 30-day evaluation period, then the patient must be followed until the SAE or AESI resolves or returns to baseline. The medical monitor may specify a longer period of time, if required to assure the safety of the patient.

Sponsor Responsibility for Reporting AEs

All AEs will be reported to regulatory authorities, IRBs/IECs, and Investigators in accordance with all applicable global laws and regulations.

22.8 Expectedness of Events

Determinations of expectedness of all AEs and SAEs will be based on the information in the Investigator's Brochure.

23 DATA 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, the Investigator's Brochure, the eCRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs. A qualified representative of the Sponsor 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.

24 INVESTIGATOR'S REGULATORY OBLIGATIONS

24.1 Institutional Review Board (IRB) / Ethics Committee (EC) Approval

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

24.2 Pre-Study Documentation

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

- An executed Clinical Trial Agreement,
- FDA Form 1572,
- Principal Investigator's Curriculum Vitae,
- Documentation of financial disclosure,
- IRB/EC approval of the protocol,
- IRB/EC approved consent form.

24.3 Informed Consent

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

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

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

Nothing in this protocol or 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.

Declaration of Helsinki

This study will be conducted in accordance with the ethical standards that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice (GCP) guidelines and the applicable regulatory requirements.

24.4 Case Report Forms (CRF)

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

24.5 Adverse Event (AE) Reporting

The Investigator agrees to report all AEs to the Sponsor as described in Section 22.6. Furthermore, the Investigator is responsible for ensuring that any co-Investigator or sub-Investigator promptly brings AEs to the attention of the Investigator. If applicable, the Investigator also is responsible for informing the participating IRB/EC of any SAEs.

24.6 Review of Source Records

The Investigator agrees that qualified representatives of the Sponsor and regulatory agencies will have the right, both during and after this study, to conduct inspections and to audit and review medical records pertinent to the clinical study as permitted by the regulations. Patients will not be identified by name in any reports stemming from the study, and confidentiality of information in medical records will be preserved. The confidentiality of the patient will be maintained unless disclosure is required by regulations. Accordingly, the following statement (or similar statement) that permits the release of the patient's medical records will be included in the informed consent document:

> *Representatives of regulatory agencies, IRB/EC, the Sponsor, and the 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.*

24.7 Monitoring of the Study

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 the eCRFs and the dispensing and inventory record (adequate time and space for these visits should be allocated by the Investigator);

- Compliance with regulations (the verification will require comparison of the source documents to the eCRFs).

24.8 Protocol Amendments

Any significant change in the study protocol will require an amendment. The Investigator and the appropriate Sponsor's medical monitor indicate their approval by signing the approval page of the amendment. Once a protocol amendment has received approval from the Sponsor, the Investigator submits it to the IRB/EC for written approval. The approval letter, signed by the IRB/EC chair, must refer specifically to the Investigator, the Sponsor's protocol number, the protocol title, the protocol amendment number, and the date of the protocol amendment. The Sponsor submits a copy of the protocol amendment to the appropriate regulatory agency/agencies. A protocol amendment may be implemented after it has been approved by the IRB/EC.

A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately, but the change must then be documented in an amendment and reported to the IRB/EC within 5 working days.

24.9 Change in Investigator

If any Investigator retires, relocates, or otherwise withdraws from conducting a study, the responsibility for maintaining records may be transferred to another person (Sponsor, IRB/EC, other Investigators) who will accept the responsibility. The Sponsor must be notified in writing and must agree to the change. An updated FDA Form 1572 will be filed with the Sponsor and the FDA for any changes in the study personnel reported in the current FDA Form 1572.

24.10 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.

24.11 Final Study Report

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

24.12 Confidentiality

All unpublished information that the Sponsor gives to the Investigator and all information generated in connection with the study shall be kept confidential and shall not be published or disclosed to a third party without the prior written consent of the Sponsor or published prior to the Sponsor's review in accordance with the terms of the Clinical Trial Agreement. When the Sponsor generates reports for presentations to regulatory agencies, one or more of the Investigators who have contributed significantly to the study will be asked to endorse the final report. The endorsement is required by some regulatory agencies. The Investigator shall not make a patent application based on the results of this study and shall not assist any third party in making such an application without the written authorization of the Sponsor.

24.13 Records Retention

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

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26 ATTACHMENTS

Attachment 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 8 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/mm3
      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)
      i. Complete Hematologic Response (CHR)
         a) WBC ≤ institutional upper limit of normal
         b) Absolute neutrophil count (ANC) ≥ 1000/mm3
         c) Platelets ≥ 100,000/ mm3
         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)
      i. 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/mm3 ≤ Platelets < 100,000/mm3; (ii) 500/mm3 ≤ ANC <1000/mm3

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, 2012) clinical practice guidelines (accessed 21 March 2014).

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 2 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.

Attachment B Prohibited Drugs with a Risk of Torsades de Pointes

The website http://www.crediblemeds.org/everyone/composite-list-all-qtdrugs/ [Accessed: 20 December 2013] lists 4 categories of QT-prolonging drugs and may be used as a guide for this protocol. Categories include "Drugs with Known TdP Risk," "Drugs with Possible TdP Risk," "Drugs with Conditional TdP Risk," and "Drugs to be Avoided by Congenital Long QT Patients." The investigator site should register (under the "For Healthcare Providers" tab) to access these categories. If the investigator site does not wish to register, a composite list, including all categories, is available.

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

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

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

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

Generic Name	Brand Name	Class/Clinical Use
Domperidone	Motilium®, Motillium®, Motinorm Costi®, Nomit®	Antinausea / nausea
Dronedarone	Multaq®	Antiarrhythmic / atrial fibrillation
Droperidol	Inapsine®, Droleptan®, Dridol®, Xomolix®	Sedative;Antinausea / anesthesia adjunct, nausea
Erythromycin	Erythrocin®, E.E.S.®, Robimycin®, Erymax®, Ery-Tab®, Eryc Ranbaxy®, Erypar®, Eryped®, Erythrocin Stearate Filmtab®, Erythrocot®, E-Base®, Erythroped®, Ilosone®, MY-E®, Pediamycin®, Zineryt®, Abboticin®, Abboticin-ES®, Erycin®, PCE Dispertab®, Stiemycine®, Tiloryth®	Antibiotic;GI stimulant / bacterial infection; increase GI motility
Escitalopram	Cipralex®, Lexapro®, Nexito®, Anxiset-E®, Exodus®, Esto®, Seroplex®, Elicea®, Lexamil®, Lexam®, Entact®, Losita®, Reposil®, Animaxen®, Esitalo®, Lexamil®	Antidepressant / major depression, anxiety disorders
Flecainide	Tambocor®, Almarytm®, Apocard®, Ecrinal®, Flécaine®	Antiarrhythmic / abnormal heart rhythm
Halofantrine	Halfan®	Antimalarial / malaria infection
Haloperidol	Haldol®, Aloperidin®, Bioperidolo®, Brotopon®, Dozic®, Duraperidol®, Einalon S®, Eukystol®, Halosten®, Keselan®, Linton®, Peluces®, Serenace®, Serenase®, Sigaperidol®	Antipsychotic / schizophrenia, agitation
Ibutilide	Corvert®	Antiarrhythmic / abnormal heart rhythm
Levomethadyl	Orlaam®	Opiate agonist / pain control, narcotic dependence
Mesoridazine	Serentil®	Antipsychotic / schizophrenia
Methadone	Dolophine®	Opiate agonist / pain control, narcotic dependence

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

Attachment C Medications that Interact with CYP3A4, 5, and 7

The list of drugs that interact with CYP3A4, 5, and 7 can be found online at http://medicine.iupui.edu/clinpharm/DDIs/Table.aspx [Accessed: 19 December 2013]. Drugs listed as strong inhibitors and inducers of CYP3A should be avoided if possible.

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

Attachment D National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)

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

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40 [Accessed: 19 December 2013]

This version of CTCAE is compatible at the AE (Adverse Event) term level where each CTCAE term is a MedDRA LLT (Lowest Level Term). CTCAE v4.0 includes 764 AE terms and 26 'Other, specify' options for reporting text terms not listed in CTCAE. Each AE term is associated with a 5-point severity scale. MedDRA v12.0 (Medical Dictionary for Regulatory Activities) Terminology.

AP24534-10-201 Amendment 5 Protocol - Clean

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Medical Monitor Approval	06-Apr-2015 11:56 GMT-04