

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203469Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type NDA  
Application Number 203469  
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Reviewer Name R. Angelo de Claro, MD  
Review Completion Date 19 November 2012

Established Name Ponatinib  
Trade Name Iclusig<sup>®</sup>  
Therapeutic Class Kinase Inhibitor  
Applicant ARIAD Pharmaceuticals, Inc.

Formulation Tablet  
Dosing Regimen 45 mg PO once a day  
Indications Patients with CP-CML, AP-CML, BP-CML, or Ph+ ALL resistant or intolerant to prior tyrosine kinase inhibitor therapy  
Intended Population ≥ 18 years of age

Template Version: [March 6, 2009](#)

## Table of Contents

<b>1</b>	<b>RECOMMENDATIONS/RISK BENEFIT ASSESSMENT .....</b>	<b>10</b>
1.1	Recommendation on Regulatory Action .....	10
1.2	Risk Benefit Assessment.....	10
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies .	12
1.4	Recommendations for Postmarket Requirements and Commitments .....	12
<b>2</b>	<b>INTRODUCTION AND REGULATORY BACKGROUND .....</b>	<b>13</b>
2.1	Product Information .....	13
2.2	Tables of Currently Available Treatments for Proposed Indications .....	14
2.3	Availability of Proposed Active Ingredient in the United States .....	15
2.4	Important Safety Issues With Consideration to Related Drugs.....	15
2.5	Summary of Presubmission Regulatory Activity Related to Submission .....	17
2.6	Other Relevant Background Information .....	17
<b>3</b>	<b>ETHICS AND GOOD CLINICAL PRACTICES.....</b>	<b>17</b>
3.1	Submission Quality and Integrity .....	17
3.2	Compliance with Good Clinical Practices .....	17
3.3	Financial Disclosures.....	18
<b>4</b>	<b>SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES .....</b>	<b>18</b>
4.1	Chemistry Manufacturing and Controls .....	18
4.2	Clinical Microbiology.....	19
4.3	Preclinical Pharmacology/Toxicology .....	19
4.4	Clinical Pharmacology .....	21
4.4.1	Mechanism of Action.....	21
4.4.2	Pharmacokinetics.....	21
<b>5</b>	<b>SOURCES OF CLINICAL DATA.....</b>	<b>22</b>
5.1	Tables of Studies/Clinical Trials .....	22
5.2	Review Strategy .....	24
5.3	Discussion of Individual Studies/Clinical Trials.....	24
<b>6</b>	<b>REVIEW OF EFFICACY .....</b>	<b>44</b>
	Efficacy Summary.....	44
6.1	Indication .....	44
6.1.1	Methods .....	45
6.1.2	Demographics.....	45
6.1.3	Subject Disposition.....	49
6.1.4	Analysis of Primary Endpoint(s).....	49
6.1.5	Analysis of Secondary Endpoints(s) .....	52
6.1.6	Other Endpoints .....	55

6.1.7	Subpopulations .....	55
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations ....	55
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	55
6.1.10	Additional Efficacy Issues/Analyses .....	56
<b>7</b>	<b>REVIEW OF SAFETY.....</b>	<b>58</b>
	Safety Summary .....	58
7.1	Methods.....	59
7.1.1	Studies/Clinical Trials Used to Evaluate Safety .....	59
7.1.2	Categorization of Adverse Events.....	59
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	60
7.2	Adequacy of Safety Assessments .....	60
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations .....	60
7.2.2	Explorations for Dose Response.....	66
7.2.3	Special Animal and/or In Vitro Testing .....	66
7.2.4	Routine Clinical Testing .....	67
7.2.5	Metabolic, Clearance, and Interaction Workup .....	67
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class ..	67
7.3	Major Safety Results .....	70
7.3.1	Deaths.....	70
7.3.2	Nonfatal Serious Adverse Events .....	72
7.3.3	Dropouts and/or Discontinuations .....	73
7.3.4	Significant Adverse Events .....	73
7.3.5	Submission Specific Primary Safety Concerns .....	90
7.4	Supportive Safety Results .....	91
7.4.1	Common Adverse Events .....	91
7.4.2	Laboratory Findings .....	93
7.4.3	Vital Signs .....	93
7.4.4	Electrocardiograms (ECGs) .....	94
7.4.5	Special Safety Studies/Clinical Trials.....	96
7.4.6	Immunogenicity.....	96
7.5	Other Safety Explorations.....	96
7.5.1	Dose Dependency for Adverse Events .....	96
7.5.2	Time Dependency for Adverse Events.....	96
7.5.3	Drug-Demographic Interactions .....	96
7.5.4	Drug-Disease Interactions.....	96
7.5.5	Drug-Drug Interactions.....	96
7.6	Additional Safety Evaluations .....	97
7.6.1	Human Carcinogenicity .....	97
7.6.2	Human Reproduction and Pregnancy Data.....	97
7.6.3	Pediatrics and Assessment of Effects on Growth .....	97
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	97

7.7	Additional Submissions / Safety Issues .....	99
<b>8</b>	<b>POSTMARKET EXPERIENCE.....</b>	<b>99</b>
<b>9</b>	<b>APPENDICES .....</b>	<b>100</b>
9.1	Literature Review/References .....	100
9.2	Labeling Recommendations .....	101
9.3	Advisory Committee Meeting.....	101

## Table of Tables

Table 1 FDA-Approved Drugs for CML or Ph+ALL .....	14
Table 2 Aqueous Buffer Solubility of Ponatinib HCl .....	19
Table 3 Mean IC50 (nM) data for 108 kinases, AP24534 Lot 7.....	20
Table 4 Clinical Trial Reports Included in NDA 203469.....	23
Table 5 Study 10-201 Cohorts .....	24
Table 6 Definition of CML Phases and Ph+ALL .....	26
Table 7 Dose Modification for Non-Hematologic Adverse Events .....	31
Table 8 Dose Modification for Hematologic Adverse Events.....	32
Table 9 Schedule of Events for Patients with CP-CML .....	35
Table 10 Schedule of Events for Patients with AP-CML, BP-CML, or Ph+ALL .....	36
Table 11 Schedule of Events for Long-term Follow-up (All Patients) .....	37
Table 12 Study 10-201 Landmarks and Protocol Amendments .....	37
Table 13 Demographics of Efficacy Population of Study 10-201.....	46
Table 14 Efficacy Population of Study 10-201: Disease History and Prior Treatments ..	47
Table 15 Concordance between T315I-mutation detection by history and centralized laboratory testing (b) (6) .....	48
Table 16 Study 10-201 Disposition (Data Cutoff Date: 27 April 2012) .....	49
Table 17 FDA and Applicant's Primary Endpoint Analysis in Patients with CP-CML ....	49
Table 18 Applicant's Primary Endpoint Analysis in Patients with AP-CML.....	50
Table 19 FDA Adjudication of Major Hematologic Response in Patients with AP-CML ..	50
Table 20 FDA Primary Endpoint Analysis in Patients with AP-CML.....	50
Table 21 Applicant's Primary Endpoint Analysis in Patients with BP-CML or Ph+ ALL ..	51
Table 22 FDA Primary Endpoint Analysis in Patients with BP-CML.....	51
Table 23 FDA Primary Endpoint Analysis in Patients with Ph+ALL.....	51
Table 24 FDA Primary Endpoint Analysis in Patients with BP-CML or Ph+ALL .....	52
Table 25 FDA Adjudication for Duration of Major Hematologic Response .....	53
Table 26 Overall Survival of Total Population (N=449) in Study 10-201 .....	54
Table 27 Protocol Violations in Study 10-201.....	56
Table 28 Study 10-201 Baseline Patient Characteristics at Study Entry .....	61
Table 29 Study 10-201 Baseline Disease Characteristics.....	62
Table 30 Study 10-201 Prior Treatment History .....	63
Table 31 Treatment Intervals for Lines of TKI therapy .....	64
Table 32 Study 10-201 Duration of Exposure and Cumulative Exposure.....	65
Table 33 Study 10-201 Analysis of Treatment Intensity .....	65
Table 34 Summary of Dose Modifications for Study 10-201 .....	66
Table 35 Summary of Dose Reductions for Study 10-201 .....	66
Table 36 Safety Summary for Study 10-201 .....	70
Table 37 Deaths on Study or Within 30 Days after Discontinuation, Excluding Progressive Disease: Study 10-201 .....	70
Table 38 Treatment-Emergent Serious Adverse Events in $\geq 2\%$ of Patients in Study 10- 201 .....	72

Table 39 Univariate Analysis of Baseline Factors Associated with Arterial Ischemic Events .....	76
Table 40 Multivariate Logistic Regression Analysis for Serious Arterial Ischemic Events .....	77
Table 41 Actual SAE Risk for Arterial Ischemic Event in Study 10-201.....	78
Table 42 Arterial Ischemic Events in Patients with CP-CML or AP-CML in Study 07-101 .....	78
Table 43 Summary of Myelosuppression-Related Events.....	82
Table 44 Study 10-201 Hypertension Serious Adverse Event.....	85
Table 45 Treatment-Emergent Adverse Events $\geq$ 10% in any Disease Cohort in Study 10-201 .....	91
Table 46 Treatment-Emergent Laboratory Abnormalities $\geq$ 10% in any Disease Cohort in Study 10-201 .....	93
Table 47 Study 07-101 Mean Change from Baseline and New Outliers by Dose Group .....	94

## Table of Figures

Figure 1 Structure of Iclusig .....	18
Figure 2 Schema for T315I Mutation Testing .....	25
Figure 3 Overall Survival in Study 10-201 (Data Cutoff April 27, 2012).....	54
Figure 4 Prior TKI Sequence in Study 10-201 Patients with CP-CML or AP-CML .....	64
Figure 5 Case Summary: Fulminant Hepatic Failure.....	81

### List of Abbreviations

Abl	Abelson kinase
AE	adverse event
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AP	accelerated phase
AST	aspartate aminotransferase
AUC	area under the concentration
Bcr	breakpoint cluster region
BMI	body mass index
BP	blast phase
CAD	coronary artery disease
CABG	coronary artery bypass graft
CBC	complete blood count
CCyR	complete cytogenetic response
CHF	congestive heart failure
CHR	complete hematologic response
CI	confidence interval
Cmax	maximum concentration
CML	chronic myelogenous leukemia
CNS	central nervous system
CP	chronic phase
CSR	clinical study report
CYP	cytochrome P450
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EF	ejection fraction
FDA	Food and Drug Administration
G-CSF	granulocyte-colony stimulating factor
GGT	gamma-glutamyl transpeptidase
GI	gastrointestinal
HSCT	hematopoietic stem cell transplant
IC50	half maximal inhibitory concentration
ICA	internal carotid artery
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
LAD	left anterior descending

LDH	lactate dehydrogenase
LLN	lower limit of normal
MaHR	major hematologic response
MCyR	major cytogenetic response
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MMR	major molecular response
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NEL	no evidence of leukemia
OS	overall survival
PCR	polymerase chain reaction
PCyR	partial cytogenetic response
PD	progressive disease
PFS	progression free survival
Ph+	Philadelphia chromosome-positive
PK	pharmacokinetics
PS	performance status
PTCA	percutaneous transluminal coronary angioplasty
QTc	corrected QT interval
QTcF	QT interval corrected using the Fridericia formula
RCA	right coronary artery
RPLS	reversible posterior leukoencephalopathy syndrome
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SRC	proto-oncogene tyrosine-protein kinase
T315I	threonine-to-isoleucine mutation at amino acid position 315
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
TKI	tyrosine kinase inhibitor
TLS	tumor lysis syndrome
tmax	time to maximum concentration
TSH	thyroid stimulating hormone
TTE	time-to-event
ULN	upper limit of normal
USPI	United States Prescribing Information
VEGFR	vascular endothelial growth factor receptor

## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

I recommend accelerated approval for Iclusig for the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) resistant or intolerant to prior tyrosine kinase inhibitor therapy.

### 1.2 Risk Benefit Assessment

The basis for accelerated approval is a single Phase 2 clinical trial, Study 10-201 (PACE trial), a single-arm, international clinical trial where the efficacy and safety of Iclusig was demonstrated in cohorts of patients with CML (all phases) or Ph+ ALL.

**Clinical Benefit.** The efficacy of Iclusig was evaluated in 444 patients enrolled in 6 cohorts according to disease type and presence of T315I mutation. A summary of the key efficacy findings based on the data cut-off date of April 27, 2012 (6 months minimum follow-up for all patients, 10 months median follow-up) are listed below:

- The primary endpoint for patients with CP-CML was Major Cytogenetic Response (MCyR). The MCyR rate was 54% (144/267) overall in patients with CP-CML; 49% (99/203) in the resistant cohort and 70% (45/64) in the T315I cohort.
- The primary endpoint for patients with AP-CML was Major Hematologic Response (MaHR). The MaHR rate was 52% (43/83) overall in patients with AP-CML; 55% (36/65) in the resistant cohort and 39% (7/18) in the T315I cohort.
- The primary endpoint for patients with BP-CML or Ph+ALL was also MaHR. The MaHR rate was 31% (19/62) in patients with BP-CML and 41% (13/32) in patients with Ph+ ALL.
- The primary endpoint results were supported by duration of response. In patients with CML, the median duration of MCyR was not reached. For patients with AP-CML, BP-CML, and Ph+ ALL, the median duration of MaHR were 9.5, 4.7, and 3.2 months respectively.

**Risk.** The safety population of Study 10-201 consisted of 449 patients. A summary of the key safety findings are listed below:

- The major safety issues identified include: arterial thromboembolic events (i.e., myocardial infarction, stroke, peripheral arterial disease), arterial stenosis, hepatic toxicity, myelosuppression, hemorrhage, pancreatitis, hypertension, congestive heart failure, supraventricular tachyarrhythmias (i.e., atrial fibrillation, atrial flutter, atrial tachycardia, supraventricular tachycardia), cardiac conduction defects including QTc prolongation, venous thromboembolism, tumor lysis syndrome, gastrointestinal perforation, compromised wound healing, and fluid retention.
- The cardiovascular safety profile for Iclusig is notable for arterial ischemic events and hypertension. Based on the July 23, 2012 updated data cut-off date, 8% of patients experienced serious ischemic events. Arterial thromboembolic events and hypertension have been reported with other kinase inhibitors that inhibit VEGF-receptor kinase activity.
- The ponatinib dose was 45 mg PO once daily. The median exposure duration was 9 months for patients with CP-CML or AP-CML, and 3 months for patients with BP-CML or Ph+ALL.
- Seventy-three percent of patients required a dose modification due to adverse events. The most common adverse events that lead to dose modification include thrombocytopenia, neutropenia, lipase elevation, rash, abdominal pain, pancreatitis, and elevated liver enzymes.
- The 120-day safety update submission (data cut-off date July 23, 2012) was notable for the following: increase in frequency of arterial thromboembolic events compared to the original submission, and two cases of fatal acute hepatic failure.

**Analysis of Condition.** CML and Ph+ ALL are life-threatening conditions. In Study 10-201, there were 89 deaths on overall survival analysis: 17 in patients with CP-CML (6%), 12 in patients with AP-CML (14%), 43 in patients with BP-CML (69%), and 17 in patients with Ph+ ALL (53%).

**Unmet Medical Need.** The efficacy of ponatinib in patients with T315I-mutant CML and Ph+ALL supports the recommendation for accelerated approval as there are no drugs approved for the treatment of T315I-mutant CML or Ph+ ALL.

### **Accelerated Approval**

The Agency has previously accepted the achievement of MCyR in patients with CP-CML and MaHR in patients with AP-CML, BP-CML, or Ph+ ALL based on 6 month follow-up as an endpoint reasonably likely to predict clinical benefit. This approach was

used in the initial accelerated approval for imatinib, dasatinib, and nilotinib; all of which have already been converted to regular approval based on submission of 24-month follow-up data. As discussed above, the proposed indication is a life-threatening condition and represents an unmet medical need.

Safety issues were observed that were unique to ponatinib as compared to the other tyrosine kinase inhibitors approved for CML or Ph+ ALL. These safety issues include arterial ischemic events, arterial stenosis, hypertension, and proteinuria. Therefore, I recommend that the Applicant submit the safety data from the ongoing Phase 3 randomized trial of ponatinib versus imatinib in patients with newly-diagnosed CP-CML (Study 12-301) in addition to the 24-month follow-up data for Study 10-201 as a requirement for conversion to regular approval.

The Applicant's proposed indication for the treatment of adult patients with CP-CML, AP-CML, BP-CML, or Ph+ ALL resistant or intolerant to prior tyrosine kinase inhibitor therapy is acceptable. Although the clinical trial population in Study 10-201 enrolled a population of patients with either T315I-mutated disease or resistant or intolerant to prior dasatinib or nilotinib, ponatinib efficacy was demonstrated in all cohorts. Consequently, the clinical review team did not consider that a companion diagnostic for detection of T315I mutation was necessary for the effective use of ponatinib. Finally, given the rapidly evolving field of treatment of CML and Ph+ ALL, a general indication of prior TKI therapy is acceptable provided that the safety issues are adequately addressed in the label.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

At the time of completion of this review, the clinical team determined that a Risk Evaluation and Mitigation Strategy (REMS) would not be required for this approval. The Applicant did not submit a REMS with the application.

### **1.4 Recommendations for Postmarket Requirements and Commitments**

At the time of completion of this review, the clinical team determined the need for the following post-marketing requirements: (1) submission of 2-year follow-up efficacy and safety results for Study 10-201 and (2) submission of the safety results from a randomized clinical trial that isolates the treatment effect of ponatinib. The reader is referred to the action letter and secondary reviews for the final list of postmarketing requirements.

## 2 Introduction and Regulatory Background

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by the dysregulated production of mature and maturing granulocytes. The leukemic cells in cells in CML typically have a distinct cytogenetic abnormality, the Philadelphia chromosome.

The National Cancer Institute estimates that 5,430 men and women (3,210 men and 2,220 women) will be diagnosed and 610 men and women will die of CML in 2012. From 2005-2009, the median age at diagnosis for chronic myeloid leukemia was 64 years of age. Approximately 2.8% were diagnosed under age 20; 7.7% between 20 and 34; 9.5% between 35 and 44; 14.0% between 45 and 54; 17.0% between 55 and 64; 18.5% between 65 and 74; 20.9% between 75 and 84; and 9.6% 85+ years of age.

Philadelphia chromosome (Ph)-positive acute lymphoblastic leukemia (ALL) is the largest genetically defined subtype in adult ALL, with about 30 percent of adults overall and 50 percent of adults with B-lineage ALL. It is estimated that 6,050 men and women (3,450 men and 2,600 women) will be diagnosed with and 1,440 men and women will die of acute lymphocytic leukemia in 2012.

The treatment of CML and Ph+ALL have been revolutionized with the advent of tyrosine kinase inhibitors (TKI). The following TKIs are FDA-approved for the treatment of CML: imatinib (2001), dasatinib (2006), nilotinib (2007), and bosutinib (2012). The following TKIs are FDA-approved for the treatment of Ph+ALL: imatinib (2001) and dasatinib (2006). FDA granted accelerated approval for omacetaxine mepesuccinate in 2012 for the treatment of adult patients with CP-CML and AP-CML with resistance and/or intolerance to two or more TKIs.

The BCR-ABL T315I mutation represents a major mechanism of resistance to TKI therapy. Nicolini et al examined the medical records of 222 patients from 9 countries to describe the clinical course of patients with CML or Ph+ALL with T315I mutation. The median overall survival from the time of T315I mutation detection was 22.4, 28.4, 4.0, and 4.9 months, respectively for patients with CP-CML, AP-CML, BP-CML, and Ph+ALL.

### 2.1 Product Information

Established Name: Ponatinib  
Trade Name: Iclusig<sup>®</sup>

Applicant: ARIAD Pharmaceuticals, Inc.

Drug Class: Tyrosine kinase inhibitor

Applicant’s Proposed Indication: For the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) resistant or intolerant to prior tyrosine kinase inhibitor therapy

Applicant’s Proposed Dosage and Administration: 45 mg PO once daily

## 2.2 Tables of Currently Available Treatments for Proposed Indications

There are four tyrosine kinase inhibitors approved for the treatment of patients with CML. These include imatinib (2001), dasatinib (2006), nilotinib (2007), and bosutinib (2012). FDA has approved other non-TKI drugs for the treatment of CML. These include busulfan, cytarabine, cyclophosphamide, interferon-alfa, mechlorethamine, and omacetaxine.

Although interferon has regular approval for patients with chronic phase CML who are minimally pre-treated, imatinib, dasatinib, and nilotinib are the standard of care for the treatment of patients with CP-CML. Imatinib, nilotinib, and dasatinib all have Category 1 recommendations in the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for front-line Philadelphia Chromosome positive CML. Interferon is rarely utilized due to associated toxicities and is of historical interest only.

Although cytarabine has regular approval for blast phase CML, the tyrosine kinase inhibitors are often used in combination with AML-type induction chemotherapy or alone followed by hematopoietic stem cell transplantation.

There are multiple drugs available for the treatment of ALL. The following TKIs are FDA-approved for the treatment of Ph+ALL: imatinib (2001) and dasatinib (2006).

**Table 1 FDA-Approved Drugs for CML or Ph+ALL**

Year of Approval	Drug	Indications
1949	Mechlorethamine	For the palliative treatment of chronic myelocytic leukemia
1954	Busulfan	For the palliative treatment of chronic myelogenous (myeloid, myelocytic, granulocytic) leukemia
1959	Cyclophosphamide	Chronic lymphocytic leukemia Chronic granulocytic leukemia (it is usually ineffective in acute blastic crisis),
1986	Interferon-Alfa	For chronic phase, Philadelphia chromosome (Ph) positive chronic myelogenous leukemia (CML) patients who are minimally pretreated (within 1 year of diagnosis).
1998	Cytarabine	Blast phase of chronic myelocytic leukemia
2001	Imatinib	1. Adults with newly diagnosed Philadelphia positive (Ph+) chronic phase (CP) chronic myeloid leukemia (CML)

Year of Approval	Drug	Indications
		2. Adults with Ph+ CP CML after failure of interferon alpha therapy 3. Children with newly diagnosed Ph+ CP CML 4. Patients with Ph+ CML in blast crisis, (BC) accelerated phase (AP), or in chronic phase after failure of interferon-alpha therapy
2006	Dasatinib	1. Newly diagnosed adults with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. 2. Adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib.
2007	Nilotinib	1. The treatment of newly diagnosed patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+CML) in chronic phase. 2. The treatment of chronic phase (CP) and accelerated phase (AP) Ph+ CML in adult patients resistant to or intolerant to prior therapy that included imatinib.
2012	Bosutinib	The treatment of adult patients with chronic, accelerated, or blast phase Ph+ chronic myelogenous leukemia (CML) with resistance or intolerance to prior therapy.
2012	Omacetaxine	Treatment of adult patients with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKIs)

### 2.3 Availability of Proposed Active Ingredient in the United States

Iclusig is a new molecular entity and is not marketed in the United States or any other country at the time of this review (July 2012 to December 2012).

### 2.4 Important Safety Issues With Consideration to Related Drugs

Ponatinib is a drug in the class known as kinase inhibitors which are used in the treatment of patients with CML or Ph+ ALL. The currently marketed TKIs (as of November 2012) used to treat CML or Ph+ ALL have the following Warnings and Precautions in the US Prescribing Information (USPI):

#### Imatinib

- Fluid retention and edema
- Hematologic toxicity
- Severe congestive heart failure and left ventricular dysfunction
- Hepatotoxicity

- Hemorrhage
- Gastrointestinal disorders
- Hypereosinophilic cardiac toxicity
- Dermatologic toxicities
- Hypothyroidism
- Toxicities from long-term use
- Tumor lysis syndrome
- Use in pregnancy
- Growth retardation in children and adolescents

### **Dasatinib**

- Myelosuppression
- Bleeding events associated with severe thrombocytopenia
- Fluid retention
- QT prolongation
- Congestive heart failure, left ventricular dysfunction, and myocardial infarction
- Pulmonary arterial hypertension
- Use in pregnancy

### **Nilotinib**

Boxed warning: Prolongs the QT interval—monitor for hypokalemia or hypomagnesemia and correct deficiencies. Sudden deaths have been reported. Avoid use of concomitant drugs known to prolong the QT interval and strong CYP3A4 inhibitors

- Myelosuppression
- QT prolongation
- Sudden deaths
- Elevated serum lipase
- Hepatotoxicity
- Electrolyte abnormalities
- Use in patients with hepatic impairment
- Tumor lysis syndrome
- Drug interactions
- Food effects
- Use in pregnancy

### **Bosutinib**

- Gastrointestinal toxicity
- Myelosuppression
- Hepatic toxicity
- Fluid retention
- Embryofetal toxicity

## **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

Pre-IND meeting occurred on 4 September 2007, which was followed by the IND submission (IND 78375) on 21 November 2007. Type B meetings occurred on 4 May 2010, 12 January 2012, 16 February 2012, 7 June 2012, and 27 June 2012. CMC meetings occurred on 10 February 2011 and 27 April 2012.

Fast track designation was granted on 30 November 2010 for patients with CML and Ph+ ALL who have a T315I BCR-ABL mutation. The expanded access protocol request was granted on 27 March 2012. The request for rolling review was granted on 13 July 2012. Part 1 of 2 of the NDA (consisting of all modules except for updated stability information) was received on 31 July 2012. Part 2 of 2 of the NDA was received on 27 September 2012.

## **2.6 Other Relevant Background Information**

None

## **3 Ethics and Good Clinical Practices**

### **3.1 Submission Quality and Integrity**

The submission contains all required components of the electronic Common Technical Document (eCTD). The overall quality and integrity of the application was acceptable.

### **3.2 Compliance with Good Clinical Practices**

#### **Study 10-201 and Study 07-101**

The protocol and its amendments, as well as the patient informed consent forms, were reviewed and approved by the Institutional Review Boards (IRBs) or Independent Ethics Committees (IECs) of the participating trial centers.

The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization (ICH), Good Clinical Practices (GCP), and, where applicable, the Food and Drug Administration (FDA) regulations (21 Code of Federal Regulations, Parts 50 and 56) for the protection of the rights and welfare of human patients participating in biomedical research.

All patients or their legal representatives voluntarily consented prior to enrollment in the study.

### Clinical Site Inspections

The following sites were inspected by the FDA Office of Scientific Investigations (OSI) as part of the NDA review:

1. University of Texas MD Anderson Cancer Center (PI: Jorge Cortes, M.D.)
2. Moffitt Cancer Center (PI: Javier Pinilla-Ibarz, M.D., Ph.D.)
3. ARIAD Pharmaceuticals.

Based on the inspection findings for the clinical sites and the NDA Applicant, OSI determined that the clinical trial data collected appeared generally reliable.

### 3.3 Financial Disclosures

The Applicant submitted financial disclosure information from all 471 investigators. Only one investigator had financial interests to disclose, (b) (6) from site (b) (6). He disclosed that he has equity in ARIAD Pharmaceuticals, Inc valued in the amount of \$120,488.56 in December 2011. Dr. (b) (6) site enrolled (b) (6) patients in Study (b) (6).

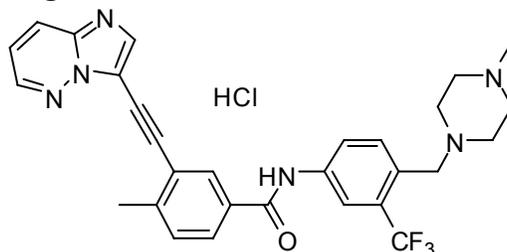
**Reviewer Comment:** The financial conflicts identified were not likely to have affected the results of the clinical trial.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

Iclusig<sup>®</sup> (ponatinib) is a kinase inhibitor. The chemical name for ponatinib is 3-(imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}benzamide hydrochloride. The molecular formula is C<sub>29</sub>H<sub>28</sub>ClF<sub>3</sub>N<sub>6</sub>O which corresponds to a formula weight of 569.02 g/mol. The structure of ponatinib is shown in Figure 1.

**Figure 1 Structure of Iclusig**



Ponatinib HCl is an off-white to yellow powder. The solubility of ponatinib in aqueous solutions decreases with increasing pH. The pKa of ponatinib is 2.77 (b) (4) and 7.8 (b) (4) within a pH range of (b) (4).

**Table 2 Aqueous Buffer Solubility of Ponatinib HCl**

USP Buffer pH	Solubility (mcg/mL)
	(b) (4)
1.7	7,790
2.7	3.44
3.7	0.28
6.7	0.50
7.5	0.16

Source: Module 3.2.S.1.3

Iclusig tablets are white, round, film-coated tablets containing ponatinib (as ponatinib HCl), with the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (type B), colloidal silicon dioxide and magnesium stearate. The tablet coating consists of talc, polyethylene glycol, polyvinyl alcohol, and titanium dioxide.

Refer to CMC and Biopharmaceutics Review for details.

## 4.2 Clinical Microbiology

CMC Microbiology review indicated that the drug product is a tablet for oral administration, and that the tablet contents (b) (4) tableting. No deficiencies were identified based upon the information provided in this application.

Clinical Microbiology consult was not required for this application.

## 4.3 Preclinical Pharmacology/Toxicology

Refer to the Pharmacology-Toxicology Review for details.

Ponatinib pharmacology was evaluated using a series of *in vitro*, cell based and *in vivo* studies results of which include:

- Ponatinib inhibits the kinase activity of native BCR-ABL or different mutant BCR-ABL proteins, including the T315I mutation, as demonstrated *in vitro* using recombinant proteins or cell-based survival assays.
- Comparative studies were conducted using ponatinib, dasatinib, nilotinib or imatinib that demonstrated ponatinib alone has activity towards inhibiting T315I mutant activity at sub-micromolar concentrations.

- Ponatinib was tested against a panel of kinases comprising approximately half of the human kinome, and it inhibited 41 kinases (other than BCR-ABL and its variants) with IC50 values  $\leq$  20 nM. These kinases include RET, FLT3, KIT and members of the VEGFR, FGFR, PDGFR, EPH and SRC families of kinases

**Reviewer Comment:** The pharmacology studies for ponatinib indicate a broad spectrum of kinase inhibition, including the VEGFR-family of kinases (refer to Table 3). The mean IC50 for FLT1/VEGFR1 was 3.7 nM. The mean IC50 for KDR/VEGFR2 was 2.9 nM.

**Table 3 Mean IC50 (nM) data for 108 kinases, AP24534 Lot 7**

IC50 $\leq$ 2 nM		IC50 $\leq$ 20 nM		IC50 $\leq$ 200 nM		IC50 >200 nM	
Kinase	IC50 (nM)	Kinase	IC50 (nM)	Kinase	IC50 (nM)	Kinase	IC50 (nM)
ABL	0.4	BLK	6.1	BMX/ETK	47	AKT2/PKBb	>1000
ABL (H396P)	0.3	CSK	12.7	BRK	51	ALK	>1000
ABL (M351T)	0.3	DDR2	16.1	EPHA1	143	Aurora A	>1000
ABL (Q252H)	0.4	EPHA2	2.1	ERBB4/HER4	176	Aurora B	543
ABL (T315I)	2.0	EPHA3	6.7	JAK1	32	Aurora C	>1000
ABL (Y253F)	0.3	EPHA7	8.5	JAK2	169	AXL	>1000
ABL2/ARG	0.8	EPHA8	2.5	JAK3	91	BTK	849
EPHA4	1.1	EPHB4	10.2	KIT (D816V)	152	BTK(E41K)	>1000
EPHA5	0.7	FGFR1	2.2	KIT (V654A)	78	CDK2/cyclin E	>1000
EPHB1	1.2	FGFR1 (V561M)	7.3	P38b	173	CTK/MATK/HYL	>1000
EPHB2/HEK5	0.6	FGFR3	18.2	P70S6K	94	EGFR	>1000
EPHB3	1.1	FGFR4	7.7	PYK2/FAK2	35	EGFR	>1000
FGFR2	1.6	FLT1/VEGFR1	3.7	TYK2	177	(L858R/T790M)	>1000
FGFR2 (N549H)	0.4	FLT3	12.6			EGFR (L858R)	211
FGR	0.5	FLT4	2.3			EGFR (L861Q)	536
FRK/PTK5	1.3	FMS	8.6			EGFR (T790M)	>1000
FYN	0.4	KDR/VEGFR2	2.9			ERBB2/HER2	>1000
HCK	0.1	KIT	12.5			FAK/PTK2	>1000
KIT (V560G)	0.4	KIT (D816H)	16.0			FER	560
LCK	0.3	P38a	9.8			FES/ FPS	768
LYN	0.2	PDGFR $\alpha$ (D842V)	15.6			FLT3 (D835Y)	948
LYNB	0.2	PDGFR $\alpha$ (T674I)	3.0			IGF1R	>1000
PDGFR $\alpha$	1.1	PDGFR $\beta$	7.7			IR	>1000
PDGFR $\alpha$ (V561D)	0.8	RAF/RAF1	13.7			IRR/INSRR	>1000
RET	0.2	RET (V804L)	3.7			ITK	>1000
RET (V804M)	1.4	SRC	5.4			MER	406
Yes	0.9	TIE2	14.3			MET	>1000
		TRKA/NTRK1	11.4			mTOR	>1000
		TRKB/NTRK2	15.1			MUSK	694
		TRKC/NTRK3	13.2			PKA	613
						PKCtheta	>1000
						RON/MST1R	>1000
						ROS	>1000
						SRC (T341M)	>1000
						SYK	>1000
						TEC	>1000
						TYK1/LTK	>1000
						TYRO3/SKY	>1000
						ZAP70	>1000

Source: Page 14, ARP280.0 Nonclinical Study Report (Module 4.2.1.1.1)

## 4.4 Clinical Pharmacology

Refer to the Clinical Pharmacology Review for details.

### 4.4.1 Mechanism of Action

Ponatinib inhibits the kinase activity of native and mutant forms of BCR-ABL tested, including the T315I mutant. Ponatinib elicited anti-tumor activity in mice bearing tumors expressing native or T315I mutant BCR-ABL. Ponatinib inhibited additional kinases with IC50 concentrations below 20 nM, including VEGFRs, FGFRs, PDGFRs and EPH receptor family members and RET, KIT, SRC, RAF and FLT3.

### 4.4.2 Pharmacokinetics

#### Absorption

Peak concentrations of ponatinib are observed approximately 4 hours after oral administration. Within the range of clinically relevant doses evaluated in patients (15-60 mg), ponatinib exhibited dose proportional increases in both Cmax and AUC. The geometric mean (CV%) Cmax and AUC(0- $\tau$ ) exposures achieved for ponatinib 45 mg daily at steady state were 77 ng/mL (50%) and 1296 ng.hr/mL (48%), respectively. Following either a high-fat and low-fat meal, plasma ponatinib exposures (AUC and Cmax) were not different versus fasting conditions. Iclusig may be administered with or without food.

#### Distribution

Ponatinib is highly bound (>99%) to plasma proteins in vitro. The blood/plasma ratio of ponatinib is 0.96. At daily doses of 45 mg, the geometric mean (CV%) apparent steady state volume of distribution is 1101 L (94%) suggesting that ponatinib is extensively distributed in the extravascular space. In vitro studies suggested that ponatinib is either not a substrate or is a weak substrate for both P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Ponatinib is not a substrate for organic anion transporting polypeptides (OATP1B1, OATP1B3) and organic cation transporter 1 (OCT1).

#### Metabolism

Ponatinib is metabolized to an inactive carboxylic acid metabolite by esterases and/or amidases, and metabolized by CYP3A4 to an N-desmethyl metabolite that is 4 times less active than ponatinib. The carboxylic acid and the N-desmethyl metabolite comprise 58% and 2% of the circulating levels of ponatinib, respectively.

#### Elimination

Following single and multiple 45 mg doses of Iclusig, the terminal elimination half-life of ponatinib was 22 hours and steady state conditions are typically achieved within 1 week

of continuous dosing. With once-daily dosing, plasma exposures of ponatinib are increased by approximately 1.5-fold between a first dose and steady state conditions. Ponatinib is mainly eliminated via feces. Following a single oral dose of [14C]-labeled ponatinib, approximately 87% of the radioactive dose is recovered in the feces and approximately 5% in the urine. Unchanged ponatinib accounted for 24% and <1% of the administered dose in feces and urine, respectively, with the remainder of the dose comprising metabolites.

#### Special Populations

Iclusig has not been studied in patients with hepatic impairment or renal impairment.

## **5 Sources of Clinical Data**

### **5.1 Tables of Studies/Clinical Trials**

The clinical studies included in this NDA are summarized in the table below.

**Table 4 Clinical Trial Reports Included in NDA 203469**

Clinical Trial ID (Study Dates)	Study Status; Type of Report	Type of Study	Design	US sites	Treatment Regimen	Number of subjects
<b>11-102</b> (Aug 2011 to Oct 2011)	Complete; Full	Food Effect	Single dose, randomized, open-label, 3-period, 6-sequence, crossover in healthy subjects	No (Study done in Canada)	Three single oral doses of 45 mg of ponatinib given in fasting state, after a high-fat meal, and after a low-fat meal	24
<b>11-104</b> (Oct 2011 to Nov 2011)	Complete; Full	ADME	Single-center, open-label, mass balance study in healthy male subjects	Yes	Single, 45 mg oral dose of [14C] ponatinib	6
<b>11-103</b> (Aug 2011 to Oct 2011)	Complete; Full	Drug Interaction	Open-label, randomized, 2-period, 2-sequence, crossover study in healthy subjects	No (Study done in Canada)	Two single, oral doses of 15 mg ponatinib, once given alone and once co-administered with ketoconazole	23
<b>07-101</b> (Start Jun 2008, enrolment completed Oct 2010)	Ongoing; Full Interim	Dose Escalation	Phase 1, open-label, 3+3 cohort, multicenter trial in adult patients with refractory or advanced CML and other hematologic malignancies	Yes	Oral once daily administration of ponatinib. Dose levels were 2 mg, 4 mg, 8 mg, 15 mg, 30 mg, 45 mg, and 60 mg.	81
<b>10-201</b> (Start Sep 2010, enrolment completed Sep 2011)	Ongoing; Full Interim	Efficacy and Safety	Phase 2, single-arm, open-label, multicenter trial in adult patients with CML or PH+ ALL who either: are resistant to either dasatinib or nilotinib or Have the T315I mutation	Yes	Oral 45 mg once daily administration of ponatinib	449

## 5.2 Review Strategy

The clinical review was primarily based on the efficacy and safety data of the Clinical Trial 10-201 (PACE Trial). An additional Phase 1 dose-escalation clinical trial (07-101) was also reviewed as support to the PACE trial safety data. The electronic submission, with the clinical study reports, and other relevant portions of NDA 203469 were reviewed and analyzed. The key review materials and activities are outlined below:

The electronic submission of the NDA;

Relevant published literature;

Relevant submissions in response to review team's information requests;

Applicant presentation slides to FDA on 6 August 2012;

Major efficacy and safety analyses reproduced or audited.

## 5.3 Discussion of Individual Studies/Clinical Trials

### 5.3.1 Protocol AP24534-10-201 (PACE trial)

#### 5.3.1.1 Study Title

A Pivotal Phase 2 Trial of Ponatinib (AP24534) in Patients with (b) (4) Chronic Myeloid Leukemia and Ph+ Acute Lymphoblastic Leukemia

#### 5.3.1.2 Study Design

This is a multi-center, international, phase 2, single-arm, open-label trial of oral ponatinib in patients with Ph+ disease.

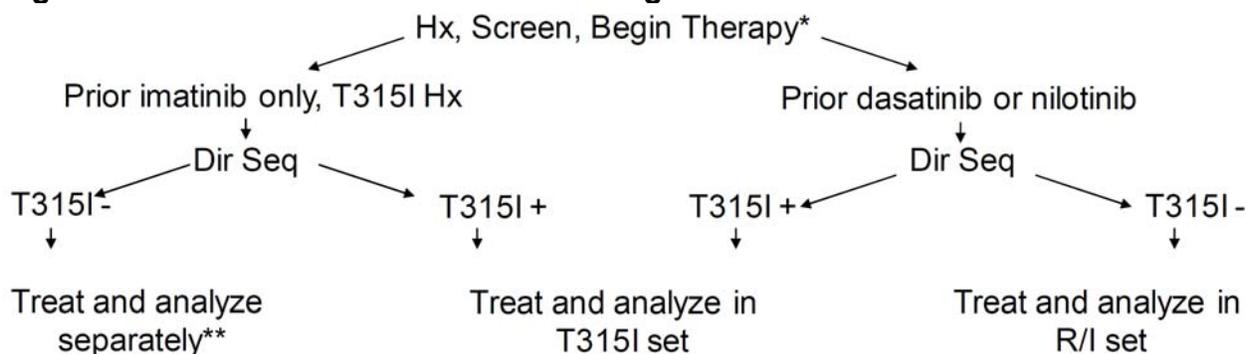
#### Trial Population

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 be grouped in the following cohorts:

**Table 5 Study 10-201 Cohorts**

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

**Figure 2 Schema for T315I Mutation Testing**



\*Obtain blood for sequencing at screen, but can begin therapy if pt meets either eligibility criterion

\*\* These patients not included in T315I set sample size calculations

Source: Study 10-201 Protocol version 1.0, page 56

#### *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 optimal. If less than 20 metaphases are examined, the BM aspirate should be repeated if possible to obtain an optimal specimen.

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 CP-CML 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).

**Table 6 Definition of CML Phases and Ph+ALL**

<b>Table 12-1 Chronic Myeloid Leukemia (CML) Phase Classification</b>	
<b>CML Phase</b>	<b>Criteria</b>
Chronic Phase (CP)	<15% blasts in peripheral blood or bone marrow <b>and</b> <20% basophils in peripheral blood <b>and</b> <30% blasts + promyelocytes in peripheral blood or bone marrow <b>and</b> $\geq 100 \times 10^9$ platelets/L in peripheral blood <b>and</b> No extramedullary disease
Accelerated Phase (AP)	$\geq 15\%$ and $< 30\%$ blasts in peripheral blood or bone marrow <b>or</b> $\geq 20\%$ basophils in peripheral blood or bone marrow <b>or</b> $\geq 30\%$ blasts + promyelocytes in peripheral blood or bone marrow (but $< 30\%$ blasts) <b>or</b> $< 100 \times 10^9$ platelets/L in peripheral blood unrelated to therapy <b>or</b> Cytogenetic, genetic evidence of clonal evolution <b>And</b> No extramedullary disease
Blast Phase (BP)	$\geq 30\%$ blasts in peripheral blood or bone marrow <b>or</b> 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.

Source: Study 10-201 Protocol version 1.0, page 54

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  $\geq 18$  years old.
5. Provide written informed consent.
6. Eastern Cooperative Oncology Group (ECOG) performance status  $\leq 2$ .
7. Minimum life expectancy of 3 months or more.
8. Adequate renal function defined as serum creatinine  $< 1.5 \times$  upper limit of normal (ULN) for institution.
9. Adequate hepatic function defined as:
  - a. Total bilirubin  $< 1.5 \times$  ULN,
  - b. Alanine aminotransferase (ALT [SGPT]) and aspartate aminotransferase (AST [SGOT])  $< 2.5 \times$  ULN for institution ( $< 5 \times$  ULN if liver involvement with leukemia),
  - c. Prothrombin time (PT)  $< 1.5 \times$  ULN.
10. Normal pancreatic status defined as:
  - a. Lipase  $\leq 1.5 \times$  ULN,
  - d. Amylase  $\leq 1.5 \times$  ULN.
11. Normal QTcF interval on screening ECG evaluation, defined as QTcF of  $\leq 450$  ms in males or  $\leq 470$  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 hydroxyurea or anagrelide within 24 hours, vincristine (for ALL only) within 7 days, or interferon or cytarabine within 14 days, or immunotherapy within 14 days, or any other cytotoxic chemotherapy, radiotherapy, or investigational therapy within 28 days prior to receiving the first dose of ponatinib, or have not recovered (> Grade 1 by 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 CP-CML are excluded if they are in CCyR.
8. Patients with AP-CML, BP-CML, 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.

### Study Treatment

Patients will receive once daily oral administration of ponatinib at a dose of 45 mg.

*Dose Delay or Dose Reductions for Adverse Events.* Table 7 and Table 8 describe the guidelines for dose modification due to study-drug-related toxicity, graded according to NCI CTCAE 4.0. In each clinical circumstance, the clinical investigator may manage patient care according to his or her clinical judgment. Moreover, with the resolution of the observed toxicity, the investigator may resume full dosing if clinically indicated.

There will be no dose modifications for grade 1 or 2 non-hematologic toxicities (except for pancreatitis) attributable to the study drug that are manageable with supportive care or do not interfere with normal daily activities of the patient. In the event of a persistent grade 1 or 2 non-hematologic adverse drug reaction that is 1) intolerable due to clinical symptoms or interferes with normal daily activities, or 2) not controlled by optimal supportive care, the patient may be managed by dose delay or reduction as described in Table 7. There are no suggested dose modifications for grade 1 or 2 hematologic toxicities.

Guidelines for assessment and management of pancreatitis are described in Table 7. Pancreatic toxicities may manifest as an isolated elevation of pancreatic enzymes (amylase, lipase) in the absence of symptoms; or by enzyme elevation coupled with clinical symptoms. In the latter case, imaging should be performed, but in the case of isolated enzyme elevations it is optional.

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. Note that grade 3 or 4 myelosuppression might be attributable to disease rather than study drug. In this case, dose reduction or delay if deemed necessary 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 7 Dose Modification for Non-Hematologic Adverse Events**

<b>Non-hematologic Toxicity</b>	
Grade 2 Persistent 7 days with optimal care	<p>Hold ponatinib</p> <p>Resume at 45 mg after recovery to <math>\leq</math> Grade 1</p> <p>Recurrence at 45 mg</p> <p>Hold ponatinib</p> <p>Resume at 30 mg after recovery to <math>\leq</math> Grade 1</p> <p>Recurrence at 30 mg</p> <p>Hold ponatinib</p> <p>Resume at 15 mg after recovery to <math>\leq</math> Grade 1</p> <p>Recurrence at 15 mg</p> <p>Consider discontinuing ponatinib</p>
Grade $\geq$ 3	<p>Hold ponatinib</p> <p>Resume at 30 mg after recovery to <math>\leq</math> Grade 1</p> <p>Recurrence at 30 mg</p> <p>Hold ponatinib</p> <p>Resume at 15 mg after recovery to <math>\leq</math> Grade 1</p> <p>Recurrence at 15 mg</p> <p>Consider discontinuing ponatinib</p>
<b>Pancreatitis with or without amylase/lipase elevation</b>	
Grade 2	<p>Hold ponatinib</p> <p>Perform ultrasound or abdominal CT scan with contrast</p> <p>If imaging positive, continue holding ponatinib and repeat according to clinical care</p> <p>If negative, or after resolution by imaging, resume at 30 mg after recovery to <math>\leq</math> Grade 1</p> <p>Recurrence at 30 mg</p> <p>Repeat above</p> <p>Consider discontinuing ponatinib</p>
Grade 3	<p>Hold ponatinib</p> <p>Perform ultrasound or abdominal CT scan with contrast</p> <p>Consult sponsor</p>
Grade 4	Discontinue ponatinib

**Table 6 Continued**

Amylase/Lipase without symptoms	
Grade $\geq$ 3	<p>Hold ponatinib</p> <p>Consider performing ultrasound or abdominal CT scan with contrast</p> <p>If imaging positive, continue holding ponatinib and repeat according to clinical care</p> <p>If negative, or after resolution by imaging, resume at 30 mg after recovery to <math>\leq</math> Grade 1</p> <p>Recurrence at 30 mg</p> <p>Repeat above</p> <p>Resume at 15 mg after recovery to <math>\leq</math> Grade 1</p> <p>Recurrence at 15 mg</p> <p>Repeat above</p> <p>Consider discontinuing ponatinib</p>

**Table 8 Dose Modification for Hematologic Adverse Events**

Hematologic	
ANC/platelets	
Grade $\geq$ 3	<p>Hold ponatinib</p> <p>Resume at 45 mg after recovery to <math>\leq</math> Grade 1</p> <p>Recurrence at 45 mg</p> <p>Hold ponatinib</p> <p>Resume at 30 mg after recovery to <math>\leq</math> Grade 1</p> <p>Recurrence at 30 mg</p> <p>Hold ponatinib</p> <p>Resume at 15 mg after recovery to <math>\leq</math> Grade 1</p> <p>Recurrence at 15 mg</p> <p>Consider discontinuing ponatinib</p>

*Concomitant Treatment.* All concomitant medications administered from the time of informed consent through the 30-day Follow-up Visit are to be reported on the appropriate electronic Case Report Form (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.

#### Permitted Treatment

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

#### 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).
- Use of any other investigational drug or device.
- Use of medications that are known to be associated with the development of Torsades de Pointes.
- Herbal preparations or related over-the-counter preparations containing herbal ingredients (eg, St. John's Wort, Blue Cohash, Estroven) either during or within 2 weeks prior to the first dose of ponatinib.
- Elective surgery requiring in-patient care.

Medications that are potent substrates, inhibitors or inducers of P450 cytochromes, in particular CYP3A4 should be avoided, but are not prohibited. Medications that prolong the QT interval should be avoided, but are not prohibited.

#### Schedule of Events

Patients with CP-CML underwent the following assessments on the specified cycle (C) and day (D):

- C1D1, C1D15, C2D1, C3D1, C4-13D1, C15D28, C18D28, end of every third cycle for C24 through C39, end of every subsequent sixth cycle to study drug discontinuation: vital signs, physical examination, assessment for hepatosplenomegaly, ECOG, CBC, serum chemistry, amylase, lipase
- C1D8 and C1D22: CBC
- C2D1: 12-lead ECG
- C2D15, C3D15: CBC, serum chemistry, amylase, lipase
- C3D28: 12-lead ECG, ECHO

- C3D28, end of C6, C9, C12, end of every third cycle for C6 through C18, and C24 through C39, end of every subsequent sixth cycle to study drug discontinuation: response assessment (BM aspirate and cytogenetic response, molecular response, additional disease assessments), molecular genetics

Patients with AP-CML, and BP-CML/Ph+ ALL underwent the following assessments:

- C1D1, C1D15, C2D1, C3D1, C4-26D1, end of every third cycle for C27 through C39, every subsequent sixth cycle to study drug discontinuation: vital signs, physical examination, assessment for hepatosplenomegaly, ECOG, CBC, serum chemistry, amylase, lipase
- C1D8, C1D22, C2D15, C3D15, C4-26D15: CBC
- C1D28: response assessment (BM aspirate and cytogenetic response)
- C2D1: 12-lead ECG
- C2D15: serum chemistry, amylase, lipase
- C2D28, End of even cycles, C4 to C24, end of every third cycle for C27 to C39 and then every subsequent sixth cycle: response assessment (BM aspirate and cytogenetic response, molecular response, additional disease assessments)
- C3D28: 12-lead ECG, ECHO
- C2D28, end of even cycles for C4 to C26, C4 to C24: molecular genetics

**Table 9 Schedule of Events for Patients with CP-CML**

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, 26
DAY	-21 to 1 <sup>1</sup>	1	8	15	22	1	15	1	15	28	1	28	28
<b>PROCEDURE</b>													
Informed Consent <sup>2</sup>	X												
Medical/Surgical History & Demographics <sup>3</sup>	X												
Cancer Diagnosis & Prior Cancer Therapy <sup>4</sup>	X												
BCR-ABL Mutation History <sup>5</sup>	X												
Vital Signs <sup>6</sup>	X	X		X		X		X			X		X
Physical Exam including Hepatosplenomegaly & ECOG Performance Status <sup>7</sup>	X	X		X		X		X			X		X
Complete Blood Count (CBC) with Differential <sup>8</sup>	X	X	X	X	X	X	X	X	X		X		X
Serum Chemistry, Amylase, Lipase <sup>9</sup>	X	X		X		X	X	X	X		X		X
Serum Triglycerides <sup>10</sup>	X												
Prothrombin Time (PT)/PTT <sup>11</sup>	X												
Pregnancy <sup>12</sup>	X												
Electrocardiogram (ECG) <sup>13</sup>	X					X				X			
Echocardiogram (ECHO) <sup>14</sup>	X									X			
Adverse Events	THROUGHOUT STUDY												
Concomitant Medications	THROUGHOUT STUDY												
<b>RESPONSE ASSESSMENT</b>													
Bone Marrow (BM) Aspirate & Cytogenetic Response <sup>15</sup>	X									X		X	X
Molecular Response <sup>16</sup>	X									X		X	X
Additional Disease Assessments <sup>17</sup>	X									X		X	X
<b>MUTATION ANALYSIS</b>													
Direct Sequencing for T315I <sup>18</sup>	X												
<b>EXPLORATORY TESTS</b>													
Allele-specific oligonucleotide (ASO) for T315I <sup>19</sup>	X												
Molecular Genetics <sup>20</sup>	X									X		X	X

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**Table 10 Schedule of Events for Patients with AP-CML, BP-CML, or Ph+ALL**

CYCLE (1 cycle = 28 days)	Screening	Cycle 1					Cycle 2			Cycle 3			Cycles 4 to 26		End of Even Cycles 4 to 26
		1	8	15	22	28	1	15	28	1	15	28	1	15	
<b>PROCEDURE</b>															
Informed Consent <sup>2</sup>	X														
Medical/Surgical History & Demographics <sup>3</sup>	X														
Cancer Diagnosis & Prior Cancer Therapy <sup>4</sup>	X														
BCR-ABL Mutation History <sup>5</sup>	X														
Vital Signs <sup>6</sup>	X	X		X			X			X			X		
Physical Exam including Hepatosplenomegaly & ECOG Performance Status <sup>7</sup>	X	X		X			X			X			X		
Complete Blood Count (CBC) with Differential <sup>8</sup>	X	X	X	X	X		X	X		X	X		X	X	
Serum Chemistry, Amylase, Lipase <sup>9</sup>	X	X		X			X	X		X			X		
Serum Triglycerides <sup>10</sup>	X														
Prothrombin Time (PT)/PTT <sup>11</sup>	X														
Pregnancy <sup>12</sup>	X														
Electrocardiogram (ECG) <sup>13</sup>	X						X					X			
Echocardiogram (ECHO) <sup>14</sup>	X											X			
Adverse Events		THROUGHOUT STUDY													
Concomitant Medications		THROUGHOUT STUDY													
<b>RESPONSE ASSESSMENT</b>															
Bone Marrow (BM) Aspirate & Cytogenetic Response <sup>15</sup>	X					X				X					X
Molecular Response <sup>16</sup>	X									X					X
Additional Disease Assessments <sup>17</sup>	X									X					X
<b>MUTATION ANALYSIS</b>															
Direct Sequencing for T3151 <sup>18</sup>	X														
<b>EXPLORATORY TESTS</b>															
Allele-specific oligonucleotide (ASO) for T3151 <sup>19</sup>	X														
Molecular Genetics <sup>20</sup>	X									X					X

**Table 11 Schedule of Events for Long-term Follow-up (All Patients)**

Procedure	Visit		Survival Follow-up <sup>22</sup>
	End-of-Treatment Visit <sup>21</sup>	Follow-up Visit <sup>21</sup>	
Vital Signs <sup>6</sup>	X	X	
Physical Exam including Hepatosplenomegaly & ECOG Performance Status <sup>7</sup>	X	X	
Complete Blood Count (CBC) with Differential <sup>8</sup>	X	X	
Serum Chemistry, Amylase, Lipase <sup>9</sup>	X	X	
Pregnancy Test (if applicable) <sup>12</sup>	X		
Electrocardiogram (ECG) <sup>13</sup>	X		
Echocardiogram (ECHO) <sup>14</sup>	X	X	
Adverse Events & Concomitant Medications	X	X	
<b>RESPONSE ASSESSMENT</b>			
Molecular Response <sup>16</sup>			
<b>MUTATION ANALYSIS</b>			
Direct Sequencing for T315I <sup>18</sup>	X		
<b>EXPLORATORY TESTS</b>			
Allele-specific oligonucleotide (ASO) for T315I <sup>19</sup>	X		
Molecular Genetics <sup>20</sup>	X		
<b>SURVIVAL FOLLOW-UP</b>			
Survival <sup>22</sup>			X

Patients will remain on treatment until disease progression or intolerance develops. Progression-free survival and overall survival data will also be collected and analyzed. Each patient will be followed for up to 24 months after first dose of ponatinib. If they remain on therapy after 24 months, they will be able to continue treatment on a companion extension study that is under development at this time.

### 5.3.1.3 Clinical trial landmarks and protocol amendments

The clinical trial landmarks and protocol amendments are summarized below.

**Table 12 Study 10-201 Landmarks and Protocol Amendments**

Date	Study 10-201 Landmark
16 Jul 2010	Original Protocol
17 Sep 2010	First patient enrolled
27 Oct 2010	Amendment 1 (11 patients enrolled prior to amendment) <ul style="list-style-type: none"> <li>• Mandated examination of 20 metaphases for patient inclusion</li> <li>• Clarified the number of days within which prior treatments are allowed prior to first dose of ponatinib taking into account phase of disease</li> <li>• Update schedule of events and corresponding footnotes for end-of-treatment assessments</li> <li>• Provided clarification on the use of dose modification guidelines for AEs attributable to study drug</li> </ul>

Date	Study 10-201 Landmark
	<ul style="list-style-type: none"> <li>• Updated guidance on dose modification for pancreatitis attributable to study drug in-line with CTCAE version 4.0</li> <li>• Included guidance on dose modification for QTcF prolongation attributable to study drug in-line with CTCAE version 4.0</li> <li>• Recommended ECG monitoring when a patient is taking concomitant medications known to prolong the QTc interval</li> <li>• Update Attachment A – response criteria</li> </ul>
8 April 2011	Amendment 2 (197 patients enrolled prior to amendment) <ul style="list-style-type: none"> <li>• Increased the overall sample size of the study to allow for over-enrollment in the resistant/intolerant cohorts to ensure full patient enrollment in the T315I cohorts. The scientific objectives of the study required meeting the minimum accrual goals for all cohorts, including the T315I cohorts. Early enrollment experience demonstrated over-availability of resistant/intolerant patients compared with T315I patients. Thus, the resistant/intolerant cohorts would fill before the T315I cohorts reach their target sample sizes; hence, the need to adjust the overall sample size.</li> <li>• Incorporated details from an administrative letter that was prepared and submitted to investigative sites in March 2011 to clarify concomitant use and administration of hydroxyurea and anagrelide</li> </ul>
26 Sep 2011	Last patient enrolled (Total enrolment 449)
24 May 2012	Amendment 3 <ul style="list-style-type: none"> <li>• Extended the duration of treatment beyond the original 2 years.</li> <li>• Decreased the number of study assessments after the initial 2 years of treatment.</li> </ul>
13 July 2012	Full Interim Study Report Date (Data cutoff 27 April 2012)

#### 5.3.1.4 Efficacy and safety evaluation

Summary statistics and analyses are provided by analysis population, by cohort, by diagnosis (i.e., CP-CML, AP-CML, BP-CML/Ph+ ALL), and, where appropriate, overall.

#### Treated Population

##### Cohorts A and B (CP-CML Patients)

This population included all patients assigned to Cohort A or B who received at least 1 dose of study drug. Chronic phase patients with a negative baseline T315I mutation result and who were resistant or intolerant to either dasatinib or nilotinib were assigned to Cohort A. Chronic phase patients with a positive baseline T315I mutation result were assigned to Cohort B. Patients who were confirmed to have no detectable T315I mutation by direct sequencing, but who were not resistant or intolerant to dasatinib or nilotinib (i.e., who had been treated with only imatinib) were not included in the treated

population (or the per protocol population described below) and were analyzed separately.

For analyses of cytogenetic response, patients with less than 20 metaphases examined at baseline (including missing baseline cytogenetic assessments), or CCyR at baseline were analyzed as non-responders in the primary analysis. For analyses of hematologic response (CHR), patients who entered the trial in CHR and continued to meet CHR criteria on study also were analyzed as responders.

#### Cohorts C through F (AP-CML and BP-CML/Ph+ ALL Patients)

This population included all patients assigned to Cohorts C through F who received at least 1 dose of study drug. AP-CML patients with a negative baseline T315I mutation result and who were resistant or intolerant to either dasatinib or nilotinib were assigned to Cohort C. AP-CML patients with a positive baseline T315I mutation result were assigned to Cohort D. BP-CML patients and Ph+ ALL patients with a negative baseline T315I mutation result and who were resistant or intolerant to either dasatinib or nilotinib were assigned to Cohort E. BP-CML patients and Ph+ ALL patients with a positive baseline T315I mutation result were assigned to Cohort F. Patients confirmed to have had no detectable T315I mutation by direct sequencing and who were not resistant or intolerant to dasatinib or nilotinib were not included in the treated population and were analyzed separately (similar to the approach described for Cohorts A and B).

For analyses of cytogenetic response, patients with less than 20 metaphases examined at baseline, CCyR at baseline, or missing baseline cytogenetic assessments were analyzed as non-responders. For analyses of hematologic response (MaHR), patients for whom baseline bone marrow blasts could not be determined were analyzed as non-responders, and patients who entered the trial in MaHR were analyzed as non-responders in the primary analysis.

### 5.3.1.5 Statistics

#### 5.3.1.5.1 Sample Size

With a cohort size of 100 patients, a minimum of 29 responders (i.e., 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 exceeded 20% and the upper bound exceeded 35%. Therefore, 100 patients were expected to 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 also planned to provide at least 98% power to distinguish between 20% and 40%, meaning 29 responses were also required, and for at least 78% power to distinguish between 30% and 45%, which required 40 responses.

With a cohort size of 100 patients, the maximum width of the exact 95% CI was approximately 20% when the MCyR rate was in the expected range of 20% to 35%. For Cohort B (T315I CP-CML patients), the null or uninteresting MCyR rate was set at 10% and the alternative MCyR rate was set at 35%. With a cohort size of 60 patients, a minimum of 14 responders had to be observed in Cohort B, in order to observe an exact 95% CI, such that the lower bound exceeded 10% and the upper bound exceeded 35%. Therefore, 60 patients were needed to 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 was 25% when the MCyR rate was in the expected range of 10% to 35%.

Cohorts C through F. The endpoint for these cohorts was MaHR. The MaHR rate was defined as the proportion of patients achieving a CHR or NEL response. The null or uninteresting MaHR rate was set at 10% and the alternative MaHR at 30%. With a cohort size of 40 patients, a minimum of 9 responders needed to be observed in Cohorts C through F in order to observe an exact 95% CI, such that the lower bound exceeded 10% and the upper bound exceeded 30%. Forty patients in each cohort provided an approximately 89% power to distinguish between the null response rate of 10% and an alternative response rate of 30% in these cohorts.

Early enrollment experience demonstrated that patients whose disease was resistant or intolerant to therapy were relatively more common than patients who carried the T315I mutation. Thus, the mutation testing schema as planned would have led to a relative over-availability of resistant and intolerant patients compared with T315I patients. Therefore, Cohorts A, C, and E were expected to fill before the T315I Cohorts B, D, and F reached their target sample sizes. Since the scientific objectives of the study required meeting the target accrual goals for the T315I cohorts (and, indeed, all cohorts), the anticipated higher relative proportion of R/I patients to T315I patients required over-enrollment of the R/I cohorts (Cohorts A, C, and E) to ensure full T315I patient enrollment.

Thus, overall enrollment was determined by the need to fill the T315I cohorts. At the time of the most recent protocol amendment, it was anticipated that the trial would require up to 450 patients to ensure reaching the planned sample sizes of the T315I cohorts. The study design planned to allow individual cohorts to be closed by the sponsor to control overall enrollment to the study. At the time of this CSR, the final enrollment was 449 patients due to the adjustment needed to fill the cohorts.

### 5.3.1.5.2 Efficacy Endpoints

#### **Primary Efficacy Endpoints**

The primary endpoint for patients with CP-CML in Cohorts A and B is Major Cytogenetic Response (MCyR). MCyR rate is defined as the proportion of patients who achieved a Complete Cytogenetic Response (CCyR) or Partial Cytogenetic Response (PCyR) after the initiation of study treatment. Patients entering the trial already in PCyR had to achieve CCyR in order to be considered a success for MCyR.

The primary endpoint for patients with AP-CML or BP-CML or patients with Ph+ ALL in Cohorts C through F is Major Hematologic Response (MaHR). The MaHR rate is defined as the proportion of patients who achieved a Complete Hematologic Response (CHR) or No Evidence of Leukemia (NEL) response after the initiation of study treatment, with 1 additional assessment, at least 28 days after the first assessment of response, at which CHR or NEL criteria were met.

#### **Secondary Efficacy Endpoints**

For Cohorts A and B, the secondary efficacy endpoints are:

- a. Hematologic responses: CHR, defined as the proportion of patients who achieved CHR that was confirmed by a CBC with differential at least 28 days after the initial criteria were met; and
- b. Cytogenetic responses: confirmed MCyR, defined as the proportion of patients who achieved a confirmed CCyR or PCyR at 2 consecutive assessments at least 4 weeks apart (for patients not in PCyR at study entry), or the proportion of patients who achieved a confirmed CCyR at 2 consecutive assessments at least 4 weeks apart (for patients in PCyR at study entry); and
- c. Molecular responses: Major Molecular Response (MMR), defined as the proportion of patients who met the criteria for MMR at least once after the initiation of study treatment.

For Cohorts C through F, the secondary efficacy endpoints are:

- d. Cytogenetic responses: CCyR, PCyR, confirmed MCyR (see definition above); and
- e. Molecular responses: MMR (see definition above).

For all patients:

- f. Time to response, 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; and

- g. Duration of response, defined as the interval between the first assessment at which the criteria for response were met until the criteria for progression were met, censored at the last date at which the criteria for response were met; and
- h. Progression-free survival, defined as the interval from the first dose of study treatment until the criteria for progression were met or death, censored at the last response assessment; and
- i. Overall survival, defined as the interval from the first dose of study treatment until death, censored at the last date at which the patient was known to be alive.

Criteria for progression:

1. Progression from CP-CML

- a. Death
- b. Development of AP-CML or BP-CML
- c. Loss of CHR (in the absence of cytogenetic response)
- d. Confirmed by development in CBCs at least 4 weeks apart
- e. Loss of MCyR
- f. Increasing WBC in patients without CHR defined by doubling of WBC to >20K on 2 occasions at least 4 weeks apart (after the first 4 weeks of therapy)

2. Progression from AP-CML

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

3. Progression from BP-CML or Ph+ALL

- a. Death
- b. Increasing blasts in peripheral blood or BM over a 4-week period

Exploratory Efficacy Endpoints

The exploratory endpoints include:

- 1. BCR-ABL sequence data collected for comparison with response to therapy
- 2. Allele-specific oligonucleotide (ASO) PCR for T315I collected and compared with T315I status by history and by direct sequencing during screening and during the treatment phase, as well as with response to therapy
- 3. Molecular genetic analyses

#### 5.3.1.5.4 Safety Analysis

Evaluation of safety and tolerability is a secondary endpoint of this study. Safety evaluations were based on the incidence, intensity, and type of AEs, and clinically significant changes in the patient's physical examination findings, vital signs and clinical laboratory results. Safety variables were tabulated and presented for all patients who received at least 1 dose of study medication (safety population). Exposure to study drug and reasons for discontinuation of study treatment were tabulated.

Safety tables and analyses categorize results by total safety population, by cohort, and by diagnosis (i.e., CP-CML, AP-CML, BP-CML/Ph+ ALL).

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA version 13.0) AE coding system for purposes of summarization. All AEs that occurred on study were listed in by-patient data listings. The AE incidence rates, as well as the frequency of occurrence of overall toxicity categorized by toxicity grades (severity), were described. All AEs starting on or after the first dose of study treatment were considered treatment-emergent. In addition, AEs were summarized by relatedness to study treatment (in the opinion of the investigator) and action taken with study treatment, including dose modifications, interruptions and discontinuation. Events that were considered related to treatment (possibly, probably, or definitely related) also were tabulated. Tabulation also was provided that enumerated AEs by severity. Deaths, serious adverse events (SAEs), and events resulting in study discontinuation were tabulated in data listings including additional relevant information on the patient.

## 6 Review of Efficacy

### **Efficacy Summary**

The efficacy of Iclusig was evaluated in 444 patients with previously treated CML (chronic phase, accelerated phase, or blast phase) or Ph+ALL enrolled in Study 10-201 (PACE trial), a single-arm Phase 2 clinical trial. Patients were enrolled in 6 cohorts according to disease type and presence of T315I mutation. A summary of the key efficacy findings based on the data cut-off date of April 27, 2012 are listed below:

- The primary endpoint for patients with CP-CML was Major Cytogenetic Response (MCyR). The MCyR rate was 54% (144/267) overall in patients with CP-CML; 49% (99/203) in the resistant cohort and 70% (45/64) in the T315I cohort.
- The primary endpoint for patients with AP-CML was Major Hematologic Response (MaHR). The MaHR rate was 52% (43/83) overall in patients with AP-CML; 55% (36/65) in the resistant cohort and 39% (7/18) in the T315I cohort.
- The primary endpoint for patients with BP-CML or Ph+ALL was also MaHR. The MaHR rate was 31% (19/62) in patients with BP-CML and 41% (13/32) in patients with Ph+ ALL.
- The primary endpoint results were supported by duration of response. In patients with CML, the median duration of MCyR was not reached. For patients with AP-CML, BP-CML, and Ph+ ALL, the median duration of response were 9.5, 4.7, and 3.2 months respectively.

### **6.1 Indication**

The Applicant's proposed indication is for the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) resistant or intolerant to prior tyrosine kinase inhibitor therapy.

### 6.1.1 Methods

The efficacy review for Iclusig included the review of the following items submitted by the Applicant (ARIAD Pharmaceuticals, Inc.):

- Clinical study report for Study 10-201 (PACE trial)
- Protocol and statistical analysis plan for Study 10-201
- Raw and derived datasets for Study 10-201
- Case report forms for Study 10-201
- Narratives for Study 10-201
- Response to information requests
- Proposed labeling for Iclusig

The data cutoff date for the efficacy analysis was 27 April 2012.

### 6.1.2 Demographics

Study 10-201 enrolled 449 patients from 68 sites worldwide: Australia, Belgium, Canada, France, Germany, Italy, South Korea, United Kingdom, United States, the Netherlands, Spain, and Sweden. U.S. patients accounted for 187 (42%) of the 449 total patients. The next top-enrolling countries were France (54 patients), Germany (38 patients), Italy (38 patients), and the United Kingdom (30 patients).

The primary efficacy analysis population consisted of 444 patients out of the total 449 patients enrolled in Study 10-201. Five patients were excluded from the primary efficacy analyses due to non-confirmation of T315I mutation using a central laboratory test, and these patients did not have prior therapy with dasatinib or nilotinib.

The baseline demographics, disease history, and prior treatment history are summarized in Table 13 and Table 14.

The median age of the efficacy population was 59 years (range 18 to 94). Male patients represented 53% of the efficacy population. Seventy-nine percent of the efficacy population were Caucasian in race. US patients represented 42% (187/444) of the efficacy population. Ninety-two percent of the patients (409/444) had a baseline ECOG performance status of 0 or 1.

The median time from time of initial diagnosis for the efficacy population was 6.1 years (range 0.3 to 28.5 years). Patients in the T315I-mutation-positive cohorts tended to have a shorter time from initial diagnosis and a lower number of prior TKI therapies. The most common exposure to prior TKI therapy in the efficacy population include: imatinib (96%), dasatinib (84%), and nilotinib (66%).

**Table 13 Demographics of Efficacy Population of Study 10-201**

	CP-CML		AP-CML		BP-CML or PH+ALL	
	R/I N=203	T315I N=64	R/I N=65	T315I N=18	R/I N=48	T315I N=46
Age (years)						
Median	61	51	60	54	54	56
Range	22 to 94	18 to 87	23 to 82	24 to 78	18 to 74	18 to 80
Groups						
<18	0	0	0	0	0	0
18 to 39	11%	17%	14%	22%	25%	35%
40 to 64	49%	55%	54%	50%	46%	37%
≥ 65	40%	28%	32%	28%	29%	28%
Gender						
Male	47%	75%	38%	61%	65%	57%
Female	53%	25%	62%	39%	35%	43%
Race						
White	86%	66%	72%	50%	81%	83%
Asian	8%	22%	12%	17%	17%	15%
Black or African American	3%	6%	11%	28%	2%	2%
Other	2%	6%	5%	6%	0	0
US patients	38%	36%	45%	33%	67%	43%
Baseline ECOG Score						
0	68%	73%	51%	67%	31%	35%
1	30%	27%	38%	33%	43%	41%
2	2%	0	11%	0	25%	24%

**Table 14 Efficacy Population of Study 10-201: Disease History and Prior Treatments**

	CP-CML		AP-CML		BP-CML or PH+ALL	
	R/I N=203	T315I N=64	R/I N=65	T315I N=18	R/I N=48	T315I N=46
Time from initial diagnosis (yrs)						
Median	7.8	4.8	7.1	6.6	4.0	1.6
Range	0.5 to 27.4	1.2 to 19.5	0.3 to 28.5	1.2 to 15.9	0.6 to 27.2	0.5 to 14.1
Median number of prior TKI therapies <sup>a</sup>	3	2	3	2.5	3	2
Prior TKI exposure						
Imatinib	97%	97%	98%	100%	96%	85%
Dasatinib	87%	64%	85%	83%	94%	93%
Nilotinib	74%	52%	72%	50%	75%	39%
Bosutinib	11%	3%	6%	0	6%	2%
Prior stem cell transplant	5%	2%	9%	11%	23%	20%
Prior chemotherapy <sup>b</sup> (excludes hydroxyurea)	33%	14%	42%	50%	63%	89%
Prior chemotherapy <sup>b</sup> (includes hydroxyurea)	67%	66%	80%	89%	85%	96%
Prior interferon therapy <sup>c</sup>	46%	20%	45%	39%	17%	9%
Number of bcr-abl mutations detected						
0	67%	0	60%	0	42%	0
1	26%	78%	31%	89%	33%	78%
2	6%	17%	6%	11%	19%	20%
3	0	5%	0	0	0	2%

(a) Includes imatinib, dasatinib, nilotinib, bosutinib

(b) Chemotherapy refers to cytotoxic chemotherapy and includes conditioning regimens for stem cell transplant.

(c) Includes interferon and peg-interferon therapy

Nine percent (40/444) of the patients in the efficacy population had a prior stem cell transplant, and was more common in patients with BP-CML or Ph+ALL as compared to patients with CP-CML or AP-CML. Forty percent (178/444) had received prior cytotoxic chemotherapy (excluding hydroxyurea).

The most common bcr-abl mutations detected ( $\geq 2\%$ ) in the efficacy population were T315I (29%), F317L (8%), E255K (4%), F359V (4%), G250E (3%), Y253H (2%), and V299L (2%).

Patients classified into the T315I cohorts were based on results of direct sequencing from a pre-treatment blood sample using a central laboratory (b) (4). History of T315I mutation was also captured in case report forms. Comparison of the T315I mutation by history, and detection of T315I mutation by the central laboratory is shown in Table 15. The sensitivity and specificity of T315I-mutation history are 92% and 87%, respectively for the total population in Study 10-201.

**Table 15 Concordance between T315I-mutation detection by history and centralized laboratory testing (b) (4)**

	T315I Result		Total
	Positive	Negative	
T315I mutation by history			
Positive	118	42	160
Negative	10	279	289
Total	128	321	449

### 6.1.3 Subject Disposition

**Table 16 Study 10-201 Disposition (Data Cutoff Date: 27 April 2012)**

	Overall (N=449)	CP-CML (N=270)	AP-CML (N=85)	BP-CML (N=62)	Ph+ ALL (N=32)
Treatment ongoing	252 (56%)	185 (69%)	56 (66%)	7 (11%)	4 (13%)
Discontinued	197 (44%)	85 (31%)	29 (34%)	55 (89%)	28 (88%)
Reason for Discontinuation					
Progressive Disease or Lack of Efficacy	90 (20%)	23 (9%)	16 (19%)	32 (52%)	20 (63%)
Adverse Event (a)	67 (15%)	36 (13%)	10 (12%)	15 (24%)	6 (19%)
Withdrawal by Subject	16 (4%)	13 (5%)	0	2 (3%)	1 (3%)
Other (b)	13 (3%)	4 (1%)	2 (2%)	5 (8%)	1 (3%)
Physician Decision	10 (2%)	8 (3%)	1 (1%)	1 (2%)	0
Non-Compliance	1 (0.2%)	1 (0.4%)	0	0	0

(a) Excludes terms related to Progressive Disease or Lack of Efficacy

(b) Twelve patients discontinued treatment in anticipation of undergoing a transplant.

At the time of the data cutoff date (27 April 2012), 56% of the patients enrolled in Study 10-201 were continuing to receive ponatinib. The most common cause for treatment discontinuation was progressive disease or lack of efficacy which led to treatment discontinuation in 20% of the patients. This rate was highest in the patients with BP-CML (52%) or Ph+ALL (63%) followed by patients with AP-CML (19%) and then patients with CP-CML (9%).

Refer to Section 7.3.3 for analysis of adverse events that lead to treatment discontinuation.

### 6.1.4 Analysis of Primary Endpoint(s)

**Table 17 FDA and Applicant's Primary Endpoint Analysis in Patients with CP-CML**

	Overall (N=267)	Resistant or Intolerant	
		R/I Cohort (N=203)	T315I Cohort (N=64)
<b>Cytogenetic Response</b>			
Major <sup>a</sup> (MCyR) % (95% CI)	54% (48, 60)	49% (42, 56)	70% (58, 81)
Complete (CCyR) % (95% CI)	44% (38, 50)	37% (31, 44)	66% (53, 77)

<sup>a</sup> Primary endpoint for CP-CML cohorts was MCyR, which combines both complete (no detectable Ph+ cells) and partial (1% to 35% Ph+ cells in at least 20 metaphases) cytogenetic responses.

The primary endpoint for patients with CP-CML was Major Cytogenetic Response (MCyR). The Applicant's and FDA analysis of MCyR for patients with CP-CML showed the same results.

**Table 18 Applicant's Primary Endpoint Analysis in Patients with AP-CML**

	Accelerated Phase CML		
	Overall (N=83)	Resistant or Intolerant	
		R/I Cohort (N=65)	T315I Cohort (N=18)
<b>Hematologic Response</b>			
Major <sup>a</sup> (MaHR) % (95% CI)	58% (47, 69)	60% (47, 72)	50% (26, 74)
Complete <sup>b</sup> (CHR) % (95% CI)	47% (36, 58)	46% (34, 59)	50% (26, 74)
<b>Major Cytogenetic Response<sup>c</sup> (MCyR) %</b> (95% CI)	39% (28, 50)	34% (23, 47)	56% (31, 79)

<sup>a</sup> Primary endpoint for AP-CML and BP-CML/Ph+ALL Cohorts was MaHR, which combines complete hematologic responses and no evidence of leukemia.  
<sup>b</sup> CHR: WBC ≤ institutional ULN, ANC ≥1000/mm<sup>3</sup>, platelets ≥100,000/mm<sup>3</sup>, no blasts or promyelocytes in peripheral blood, bone marrow blasts ≤5%, <5% myelocytes plus metamyelocytes in peripheral blood, basophils <5% in peripheral blood, No extramedullary involvement (including no hepatomegaly or splenomegaly).  
<sup>c</sup> MCyR combines both complete (no detectable Ph+ cells) and partial (1% to 35% Ph+ cells in at least 20 metaphases) cytogenetic responses.

**Table 19 FDA Adjudication of Major Hematologic Response in Patients with AP-CML**

SUBJID	Cohort	Applicant's analysis	FDA analysis	Justification
938-012	AP R/I	MaHR (NEL)	Non-responder	MaHR at baseline
948-007	AP T315I	MaHR (CHR)	Non-responder	No labs or bone marrow prior to first dose.
955-002	AP R/I	MaHR (NEL)	Non-responder	No labs or bone marrow prior to first dose.
956-001	AP R/I	MaHR (CHR)	Non-responder	MaHR at baseline
957-010	AP T315I	MaHR (CHR)	Non-responder	MaHR at baseline

**Table 20 FDA Primary Endpoint Analysis in Patients with AP-CML**

	Accelerated Phase CML		
	Overall (N=83)	Resistant or Intolerant	
		R/I Cohort (N=65)	T315I Cohort (N=18)
<b>Hematologic Response</b>			
Major <sup>a</sup> (MaHR) % (95% CI)	52% (41, 63)	55% (43, 68)	39% (17, 64)
Complete <sup>b</sup> (CHR) % (95% CI)	43% (33, 55)	45% (32, 57)	39% (17, 64)

The primary endpoint for patients with AP-CML was Major Hematologic Response (MaHR). Discrepancies between the Applicant's and FDA analysis of MaHR in patients with AP-CML are explained in Table 19. The FDA analysis of hematologic response in patients with AP-CML is displayed in Table 20.

**Table 21 Applicant's Primary Endpoint Analysis in Patients with BP-CML or Ph+ ALL**

	Blast Phase CML or Ph+ ALL		
	Overall (N=94)	Resistant or Intolerant	
		R/I Cohort (N=48)	T315I Cohort (N=46)
<b>Hematologic Response</b>			
Major <sup>a</sup> (MaHR) % (95% CI)	34% (25, 45)	35% (22, 51)	33% (20, 48)
Complete <sup>b</sup> (CHR) % (95% CI)	26% (17, 36)	27% (15, 42)	24% (13, 39)
<b>Major Cytogenetic Response<sup>c</sup> (MCyR) % (95% CI)</b>	31% (22, 41)	27% (15, 42)	35% (21, 50)

<sup>a</sup> Primary endpoint for AP-CML and BP-CML/Ph+ALL Cohorts was MaHR, which combines complete hematologic responses and no evidence of leukemia.  
<sup>b</sup> CHR: WBC ≤ institutional ULN, ANC ≥1000/mm<sup>3</sup>, platelets ≥100,000/mm<sup>3</sup>, no blasts or promyelocytes in peripheral blood, bone marrow blasts ≤5%, <5% myelocytes plus metamyelocytes in peripheral blood, basophils <5% in peripheral blood, No extramedullary involvement (including no hepatomegaly or splenomegaly).  
<sup>c</sup> MCyR combines both complete (no detectable Ph+ cells) and partial (1% to 35% Ph+ cells in at least 20 metaphases) cytogenetic responses.

**Table 22 FDA Primary Endpoint Analysis in Patients with BP-CML**

	Blast Phase CML		
	Overall (N=62)	Resistant or Intolerant	
		R/I Cohort (N=38)	T315I Cohort (N=24)
<b>Hematologic Response</b>			
Major (MaHR) % (95% CI)	31% (20, 44)	32% (18, 42)	29% (13, 51)
Complete (CHR) % (95% CI)	21% (12, 33)	24% (11, 40)	17% (5, 37)

**Table 23 FDA Primary Endpoint Analysis in Patients with Ph+ALL**

	Ph+ ALL		
	Overall (N=32)	Resistant or Intolerant	
		R/I Cohort (N=10)	T315I Cohort (N=22)
<b>Hematologic Response</b>			
Major (MaHR) % (95% CI)	41% (24, 59)	50% (19, 81)	36% (17, 59)
Complete (CHR) % (95% CI)	34% (19, 53)	40% (12, 74)	32% (14, 55)

**Table 24 FDA Primary Endpoint Analysis in Patients with BP-CML or Ph+ALL**

Hematologic Response	Blast Phase CML (N=62)	Ph+ ALL (N=32)
Major (MaHR) % (95% CI)	31% (20, 44)	41% (24, 59)
Complete (CHR) % (95% CI)	21% (12, 33)	34% (19, 53)

The primary endpoint for patients with BP-CML or Ph+ALL was MaHR. The Applicant's primary endpoint analysis for patients with BP-CML or Ph+ ALL is shown in Table 21 and combined the results from patients with BP-CML and patients with Ph+ ALL. The FDA primary endpoint analysis for patients with blast-phase CML and patients with Ph+ALL are shown in Table 22, Table 23, and Table 24.

**Reviewer Comment (1):** The FDA primary endpoint analysis separated the results of patients with BP-CML from patients with Ph+ ALL due to differences in underlying disease biology and also for consistency with prior FDA action with regards to labeling prior TKI approvals for BP-CML and Ph+ ALL. In addition, 82% of the patients (51/62) with BP-CML had myeloid blast phase, 18% had lymphoid blast phase, which further supports the separated efficacy and safety analyses of patients with Ph+ALL from patients with BP-CML.

**Reviewer Comment (2):** Further subgrouping of patients with BP-CML or Ph+ALL to resistant/intolerant or T315I cohorts lead to small patient numbers and do not provide additional information beyond data as presented in Table 24.

### 6.1.5 Analysis of Secondary Endpoints(s)

#### Duration of Response

*CP-CML.* The median duration of MCyR was not reached in patients with CP-CML. Only 6 of the 144 patients with CP-CML who achieved MCyR had an event (disease progression or loss of response).

*AP-CML.* The median duration of MaHR was 9.5 months (95%CI; 5.5, 17.7 months) in the 43 patients with AP-CML who achieved MaHR. Twenty-one of the 43 patients (49%) experienced an event.

*BP-CML.* The median duration of MaHR was 4.7 months (95%CI; 2.7, NE) in patients with BP-CML who achieved MaHR. Nine of the 19 patients (47%) who achieved a response experienced an event.

*Ph+ ALL.* The median duration of MaHR was 3.2 months (95%CI; 1.8, 4.7) in patients with Ph+ ALL who achieved MaHR. Twelve of the 13 patients (92%) who achieved a response experienced an event.

**Table 25 FDA Adjudication for Duration of Major Hematologic Response**

SUBJID	Cohort	Applicant's analysis	FDA adjudication	Justification*
008-002	Ph+ ALL R/I	Censored on D127	Event on D96	Investigator-assessed PD on D96, received cytarabine and mitoxantrone starting on D101, death due to PD on D <sup>(b) (6)</sup>
017-010	Ph+ ALL T315I	Censored on D176	Event on D117	Investigator-assessed PD on D117
048-007	BP-CML T315I	Censored on D100	Event on D67	Investigator-assessed PD on D67, received cytarabine and mitoxantrone starting on D69, death due to PD on D <sup>(b) (6)</sup>
078-001	BP-CML T315I	Censored on D114	Event on D84	Investigator-assessed PD on D84, received cytarabine and daunorubicin starting on D99
128-003	AP-CML R/I	Censored on D195	Event on D164	Investigator-assessed PD on D164, received busulfan, flurabine, and ATG conditioning starting on D169

\*In all cases, the last dose of ponatinib was on the date of investigator-assessed PD.  
Note: Reference date is first dose date of ponatinib.

**Reviewer Comment:** The FDA and Applicant analyses for duration of major hematologic response (DOMAHR) were different due to the data handling of investigator assessments for progression. The Applicant excluded investigator assessment of progression in their DOMAHR analyses, while the FDA included the investigator assessments. Censoring patients prior to investigator-assessed progression lead to informative censoring: As shown in Table 25, the patients assessed to have investigator-assessed progression underwent subsequent chemotherapy, and 2 patients died subsequently from PD. Finally, FDA included the investigator assessments for progression because the cohort assignments for Study 10-201 used investigator assessments in addition to objective data.

## Overall Survival

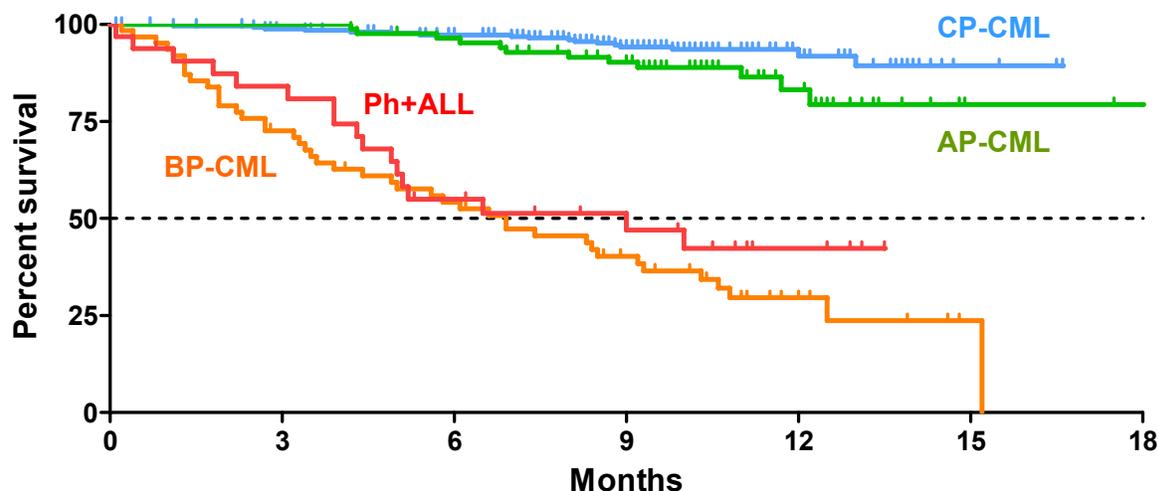
Time-to-event endpoints should be interpreted with caution in single-arm clinical trials. Analysis of overall survival are shown in Table 26 and Figure 3.

**Table 26 Overall Survival of Total Population (N=449) in Study 10-201**

Disease Cohort	N	Deaths	Median OS, in months (95%CI)	12-month OS
CP-CML	270	17 (6%)	NE	94%
AP-CML	85	12 (14%)	NE	86%
BP-CML	62	43 (69%)	6.9 (3.9, 9.3)	31%
Ph+ ALL	32	17 (53%)	9.0 (4.4, NE)	47%

NE, not estimable

**Figure 3 Overall Survival in Study 10-201 (Data Cutoff April 27, 2012)**



**Other Endpoints:** Molecular Response, Hematologic response (CP-CML), Cytogenetic response (AP-CML, BP-CML, Ph+ ALL), Progression-free survival

**Reviewer Comment (1) :** Major molecular response data cannot be adequately evaluated in Study 10-201 because performance data for the RQ-PCR assay was not submitted in the application.

**Reviewer Comment (2)** Hematologic response was not evaluable in patients with CP-CML because 42% of the patients (113/267) were already in complete hematologic response at baseline. The results for complete cytogenetic response are shown in Table 17.

**Reviewer Comment (3):** Major cytogenetic response cannot be adequately evaluated in patients with AP-CML, BP-CML, or Ph+ALL because not all patients who achieved MCyR were in hematologic response. The clinical significance of achieving MCyR in patients without hematologic response is unknown.

**Reviewer Comment (4):** Progression-free survival cannot be adequately evaluated in single-arm clinical trials due to confounding effects of the natural history of the disease. In addition, the clinical significance of PFS in the CML or Ph+ALL population is unknown. Overall survival was analyzed because OS is also a safety endpoint.

#### 6.1.6 Other Endpoints

Refer to Section 6.1.5

#### 6.1.7 Subpopulations

The small size (N=444) of the efficacy population which was further subdivided into 6 cohorts limits the ability to perform subpopulation analysis of each cohort.

#### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Analysis of efficacy data from the Phase 1 dose-escalation clinical trial, Study 07-101 is problematic due to the small number of patients treated overall and per dose cohort. Study 07-101 enrolled a total of 81 patients treated at the following dose cohorts: 2 mg (N=3), 4 mg (N=6), 8 mg (N=7), 15 mg (N=8), 30 mg (N=7), 45 mg (N=31), and 60 mg (N=19). In addition, intra-patient dose escalation was permitted in the lower dose cohorts after the maximum tolerated dose was determined.

#### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Refer to the analysis of duration of response in Section 6.1.5.

### 6.1.10 Additional Efficacy Issues/Analyses

#### Data Integrity

Twenty-nine percent (131/449) of the patients in Study 10-201 had at least one protocol violation. Refer to Table 27 for the distribution of the types of protocol deviations in Study 10-201.

**Table 27 Protocol Violations in Study 10-201**

<b>Protocol Deviation</b>	<b>Number of Patients</b>	<b>Details</b>
Inclusion criterion	61 (14%)	<ul style="list-style-type: none"> <li>- Bone marrow/cytogenetics inadequate (25 pts)</li> <li>- Bone marrow analysis not done within 42 days of</li> <li>- Enrolled as CP but is AP (6 pts)</li> <li>- Platelets not recovered from prior therapy (4 pts)</li> <li>- Elevated lipase and/or amylase (6 pts)</li> <li>- Elevated hepatic enzymes (3 pts)</li> <li>- Serum bilirubin greater than 1.5 X ULN (3 pts)</li> <li>- No ECG during screening (2 pts)</li> <li>- Pregnancy test done out of window (2 pts)</li> <li>- Prolonged QTcF (2 pts)</li> <li>- Serum creatinine &gt; 1.5 X ULN (2 pts)</li> </ul> <p><i>1 patient each</i></p> <ul style="list-style-type: none"> <li>- Enrolled in MaHR (AP)</li> <li>- Grade 2 AE from prior therapy</li> <li>- Inadequate CBC</li> <li>- Inadequate time since prior therapy</li> <li>- Lipase and amylase not done</li> <li>- No Ph+ metaphases in patient with ALL by conventional banding but positive by FISH</li> </ul>
Exclusion criterion	15 (3%)	<ul style="list-style-type: none"> <li>- Triglycerides greater than 450 mg/dL (4 pts)</li> <li>- Another primary malignancy within past 3 years (2 pts)</li> <li>- Has a history of pancreatitis or alcohol abuse (2 pts)</li> <li>- Ongoing infection (2 pts)</li> </ul> <p><i>1 patient each</i></p> <ul style="list-style-type: none"> <li>- Active CNS disease</li> <li>- History of cardiac disease within 3 months</li> <li>- History of hepatitis</li> <li>- Platelets not recovered from prior treatment</li> <li>- Pleural effusion (grade 2)</li> </ul>
Incorrect dose modification	22 (5%)	<ul style="list-style-type: none"> <li>- Restarted incorrectly after dose interruption (11 pts)</li> <li>- No dose interruption or decrease for AE (8 pts)</li> <li>- Prolonged interruption (3 pts)</li> </ul>
Inadequate screening	11 (2%)	<ul style="list-style-type: none"> <li>- No echocardiogram during screening (6 pts)</li> </ul> <p><i>1 patient each</i></p>

Protocol Deviation	Number of Patients	Details
		<ul style="list-style-type: none"> <li>- CO2/bicarbonate, PT, PTT not done</li> <li>- INR and triglycerides not done</li> <li>- INR, triglycerides and amylase not done</li> <li>- PTT not done</li> <li>- Screening echocardiogram performed outside of window</li> </ul>
Prohibited treatment	8 (2%)	<ul style="list-style-type: none"> <li>- Received other therapy outside of window (13 pts)</li> <li>- Intrathecal therapy (3 pts)</li> <li>- Radiation therapy while on trial (2 pts)</li> <li>- Taking clarithromycin (2 pts)</li> <li><i>1 patient each</i></li> <li>- Using fluorouracil cream while on trial</li> <li>- Received TKI therapy within 7 days of start of ponatinib</li> </ul>
Conduct of trial	9 (1%)	<ul style="list-style-type: none"> <li>- Screening done outside of window (8 pts)</li> <li><i>1 patient each</i></li> <li>- Continuation on trial despite multiple episodes of non-compliance (missed 14 visits)</li> <li>- Started treatment outside of window</li> </ul>
Informed consent	4 (1%)	<ul style="list-style-type: none"> <li>- No written informed consent (2 pts)</li> <li>- Bone marrow biopsy obtained before consent (1 pt)</li> <li>- Not signed by patient; Arabic translation signed by patient (1 pt)</li> </ul>
Incorrect dose	1 (<1%)	<ul style="list-style-type: none"> <li>- Patient given 60 mg instead of 45 mg</li> </ul>

**Reviewer Comment:** The above protocol deviations do not change the overall benefit-risk assessment for Iclusig. Protocol deviations that involved efficacy assessments were considered in the FDA efficacy analysis, and results were adjusted accordingly.

## 7 Review of Safety

### Safety Summary

The safety profile of Iclusig was evaluated in 449 patients with previously treated CML (all phases) or Ph+ALL enrolled in the Study 10-201, a single-arm Phase2 clinical trial. A summary of the key safety findings based on the original data cut-off date of April 27, 2012 are listed below:

- The ponatinib dose was 45 mg PO once daily. The median exposure duration was 9 months for patients with CP-CML or AP-CML, and 3 months for patients with BP-CML or Ph+ALL.
- The major safety issues identified include: arterial thromboembolic events (i.e., myocardial infarction, stroke, peripheral arterial disease), arterial stenosis, hepatic toxicity, myelosuppression, hemorrhage, pancreatitis, hypertension, congestive heart failure, supraventricular tachyarrhythmias (i.e., atrial fibrillation, atrial flutter, atrial tachycardia, supraventricular tachycardia), cardiac conduction defects including QTc prolongation, venous thromboembolism, tumor lysis syndrome, gastrointestinal perforation, compromised wound healing, and fluid retention.
- The cardiovascular safety profile for Iclusig is notable for arterial ischemic events. Based on the July 23, 2012 updated data cut-off date, 8% of patients experienced serious ischemic events. Arterial thromboembolic events have been reported with other kinase inhibitors that inhibit VEGF-receptor kinase activity.
- Seventy-three percent of patients required a dose modification due to adverse events. The most common adverse events that lead to dose modification include thrombocytopenia, neutropenia, lipase elevation, rash, abdominal pain, pancreatitis, and elevated liver enzymes.
- The 120-day safety update submission (data cut-off date July 23, 2012) was notable for the following: increase in frequency of arterial thromboembolic events compared to the original submission, and two cases of fatal acute hepatic failure.

The safety profile for Iclusig cannot be adequately evaluated in the single-arm clinical trials submitted in this application. Further characterization of the safety profile of Iclusig will be evaluated with the ongoing Phase 3 randomized active-controlled trial of Iclusig versus imatinib in patients with newly-diagnosed CML.

## 7.1 Methods

The safety population was defined as all patients who received at least 1 dose of study medication. Adverse events (AEs) and concomitant medications were collected from the time of informed consent through the 30-day Follow-up Visit.

Safety evaluations were based on the incidence, intensity, and type of AEs, and clinically significant changes in the patient's physical examination findings, vital signs and clinical laboratory results. Exposure to study drug and reasons for discontinuation of study treatment were tabulated. Refer to Table 9, Table 10, and Table 11 for schedule of assessments for AEs, physical exam, laboratory tests, and other study procedures.

All AEs that occurred on study were listed in by-patient data listings. The AE incidence rates, as well as the frequency of occurrence of overall toxicity categorized by toxicity grades (severity) were described. All AEs starting on or after the first dose of study treatment were considered treatment-emergent. In addition, AEs were summarized by relatedness to study treatment (investigator-assessment) and the action taken with study treatment, including dose modifications, interruptions and discontinuation. Deaths, serious adverse events (SAEs), and events resulting in study discontinuation were tabulated in data listings including additional relevant information on the patient.

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety review for Iclusig included the review of the following items submitted by the Applicant (ARIAD Pharmaceuticals, Inc.):

- Clinical study report for Study 10-201 (PACE trial)
- Clinical study report for Study 07-101
- Protocol and statistical analysis plan for Study 10-201 and Study 07-101
- Summary of clinical safety
- Integrated summary of safety
- Raw and derived datasets for Study 10-201 and Study 07-101
- Case report forms for Study 10-201
- Narratives for Study 10-201 and Study 07-101
- Response to information requests
- Proposed labeling for Iclusig
- 120-day safety update report

### 7.1.2 Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA version 13.0) AE coding system for purposes of summarization. AEs were

graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, v. 4.0).

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pooled analysis of the adverse events in Study 07-101 and 10-201 was performed to increase the sensitivity of detecting the adverse events. The Applicant had recoded the adverse events in both Study 07-101 and 10-201 to MedDRA version 15.0. The Applicant was not able to recode CTCAE grading to the same scale due to inherent differences in versions of the CTCAE versions.

**Reviewer Comment:** The safety profile for ponatinib in the ISS AE dataset showed similar results to the analysis of common adverse events in Study 10-201 displayed in Section 7.4 (Table 45). This is not unexpected because 449/530 (85%) of the patients in the ISS dataset were patients from Study 10-201.

## 7.2 Adequacy of Safety Assessments

The data submitted to this NDA is adequate to perform the safety review. Raw and derived datasets were provided so that pertinent analyses could be repeated by this reviewer. Verbatim AE terms were provided.

The data cutoff date for the safety analysis was 27 April 2012.

**Reviewer Comment:** The data cut-off date of 27 April 2012 was used for analyses in Section 7, with the exception of Section 7.3.4 which included the safety data from the 120-day safety update with a data cut-off date of 23 July 2012.

The median duration of follow-up for Study 10-201 was 10 months with a range of 0.1 to 18.4 months. The median duration of follow-up for the disease cohorts were 10 months (CP-CML), 10 months (AP-CML), 6 months (BP-CML), and 6 months (Ph+ALL).

FDA Office of Scientific Investigations conducted inspections at the Applicant's site and two clinical sites to verify the integrity of the data. Refer to Section 3.2 for the Summary of OSI findings.

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

#### Demographics of the Safety Population

The safety population for Study 10-201 consisted of 449 patients who received at least 1 dose of the study medication. The demographics and baseline disease

characteristics are presented in Table 28 for the overall safety population and also according to disease cohort (CP-CML, AP-CML, BP-CML, and Ph+ ALL).

**Reviewer Comment:** The safety analyses for patients with BP-CML were separated from those patients with Ph+ALL due to differences in the underlying disease biology, treatment history (refer to Table 30), and also for consistency with prior FDA action with regards to labeling prior TKI approvals for BP-CML and Ph+ ALL. In addition, 82% of the patients (51/62) with BP-CML had myeloid blast phase, 18% had lymphoid blast phase, which further supports the separated safety analyses of patients with Ph+ALL from patients with BP-CML.

Both genders were represented in Study 10-201. In general, there was a male preponderance in the overall population and disease cohorts except for accelerated phase CML where there was a female preponderance.

**Table 28 Study 10-201 Baseline Patient Characteristics at Study Entry**

	<b>Overall (N=449)</b>	<b>CP-CML (N=270)</b>	<b>AP-CML (N=85)</b>	<b>BP-CML (N=62)</b>	<b>Ph+ ALL (N=32)</b>
Gender					
Male	53%	53%	44%	60%	62%
Female	47%	47%	56%	40%	38%
Age (years)					
Median	59	60	60	53	62
Range	18 to 94	18 to 94	23 to 82	18 to 74	20 to 80
Groups					
<18	0	0	0	0	0
18 to 39	16%	12%	15%	29%	31%
40 to 64	49%	50%	53%	48%	28%
≥ 65	35%	37%	32%	23%	41%
Race					
White	78%	81%	67%	74%	97%
Asian	13%	12%	14%	23%	3%
Black or African- American	6%	4%	14%	3%	0
Other or Unknown	3%	3%	5%	0	0
ECOG PS					
0	59%	70%	55%	32%	34%
1	44%	29%	36%	35%	53%
2	8%	1%	8%	31%	13%
3	0.2%	0	0	2%	0
Body Weight (kg)					
Mean (SD)	77 (19)	80 (19)	76 (18)	71 (18)	73 (17)
Range	40 to 174	42 to 174	44 to 147	40 to 118	47 to 112

The median age of the patients was 59 years in the overall population. There were no patients younger than 18 years of age. The age range was 18 to 94 in the overall population. There were more patients in the 18 to 39 year age group or ECOG PS 2 group in the BP-CML and Ph+ ALL cohorts as compared to CP-CML or AP-CML.

The mean body weight at study entry for the overall population was 77 kg. Body weight at study entry ranged from 40 to 174 kg.

**Baseline Disease Characteristics of the Safety Population**

The baseline disease characteristics and prior treatment history demonstrate a heavily-pretreated population. The median time from initial diagnosis for the overall population was 6.1 years.

Fifty-five percent of all patients were documented to have a bcr-abl mutation at study entry. The most common bcr-abl mutations detected ( $\geq 2\%$ ) in the safety population (N=449) include T315I (29%), F317L (8%), E255K (4%), F359V (4%), G250E (3%), Y253H (2%), E255V (2%), and V299L (2%).

**Table 29 Study 10-201 Baseline Disease Characteristics**

	<b>Overall (N=449)</b>	<b>CP-CML (N=270)</b>	<b>AP-CML (N=85)</b>	<b>BP-CML (N=62)</b>	<b>Ph+ ALL (N=32)</b>
Time from initial diagnosis (years)					
Median	6.1	7.0	7.0	4.0	1.5
Range	0.3 to 28.5	0.5 to 27.4	0.3 to 28.5	0.5 to 27.2	0.5 to 7.8
Splenomegaly	13%	9%	20%	27%	6%
Hepatomegaly	5%	4%	6%	10%	3%
Baseline cytopenias (any grade)					
Thrombocytopenia	46%	31%	47%	87%	88%
Neutropenia	28%	20%	38%	48%	53%
Anemia	50%	35%	61%	85%	84%
Baseline cytopenias (Grade 3-4)					
Thrombocytopenia	33%	5%	30%	65%	64%
Neutropenia	38%	23%	29%	60%	59%
Anemia	7%	2%	10%	13%	7%
Confirmed T315I mutation, N (%)	128 (29%)	64 (24%)	18 (21%)	24 (39%)	22 (69%)

	<b>Overall (N=449)</b>	<b>CP-CML (N=270)</b>	<b>AP-CML (N=85)</b>	<b>BP-CML (N=62)</b>	<b>Ph+ ALL (N=32)</b>
Number of bcr-abl mutations detected					
0	44%	51%	47%	27%	9%
1	43%	38%	44%	53%	59%
2	11%	9%	7%	16%	25%
3	1%	1%	0	0	3%
Not evaluable	1%	0	2%	3%	3%

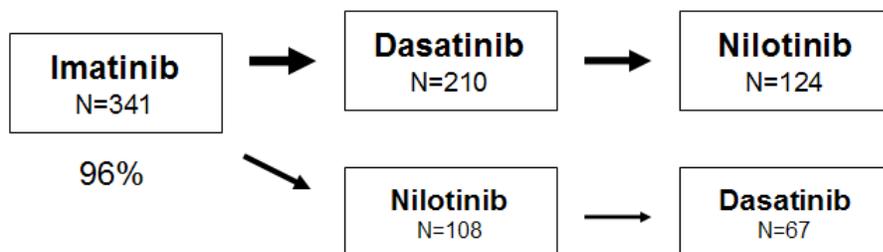
**Table 30 Study 10-201 Prior Treatment History**

	<b>Overall (N=449)</b>	<b>CP-CML (N=270)</b>	<b>AP-CML (N=85)</b>	<b>BP-CML (N=62)</b>	<b>Ph+ ALL (N=32)</b>
Median number of prior TKIs*	3	3	3	3	2
Number of prior TKIs*					
1	7%	7%	6%	5%	19%
2	37%	36%	39%	35%	44%
3	51%	52%	52%	55%	38%
4	4%	4%	4%	5%	0%
Prior TKI therapy					
Imatinib	96%	97%	99%	94%	84%
Dasatinib	84%	80%	82%	94%	94%
Nilotinib	65%	68%	66%	41%	41%
Bosutinib	7%	9%	6%	6%	0
Prior stem cell transplant	9%	4%	9%	18%	28%
Prior chemotherapy** (excludes hydroxyurea)	41%	29%	44%	65%	97%
Prior chemotherapy** (includes hydroxyurea)	75%	67%	82%	87%	97%
Prior interferon	35%	40%	45%	19%	0

\*includes imatinib, dasatinib, nilotinib, or bosutinib

\*\* Most common chemotherapy exposure (≥2%): hydroxyurea (56%), cytarabine (27%), cyclophosphamide (9%), omacetaxine (9%), vincristine (7%), methotrexate (7%), busulfan (5%), doxorubicin (5%), dexamethasone (4%), daunorubicin (4%), fludarabine (4%), idarubicin (4%), mercaptopurine (4%), prednisone (3%), asparaginase (3%), etoposide (3%)

**Figure 4 Prior TKI Sequence in Study 10-201 Patients with CP-CML or AP-CML**



**Table 31 Treatment Intervals for Lines of TKI therapy**

Interval Start	Interval End	Resistant Intolerant Cohort	T315I cohort
Initial diagnosis	Start of secondline TKI therapy	3.6 years	2.5 years
Initial diagnosis	Start of thirdline TKI therapy	6.5 years	5.5 years
Start of secondline TKI therapy	Start of thirdline TKI therapy	1.7 years	1.3 years

Patients had received a median of 3 of the following FDA-approved TKIs (imatinib, dasatinib, nilotinib, and bosutinib). The most common prior approved TKI exposure include: imatinib (96%), dasatinib (84%), and nilotinib (65%).

The summary of prior TKI sequence in Study 10-201 patients with CP-CML or AP-CML is shown in Figure 4. Ninety-six percent of the patients had imatinib as the first-line therapy. Dasatinib was the most frequent second-line therapy, followed by nilotinib. The treatment intervals for the lines of TKI therapy are shown in, and demonstrate shorter intervals in patients in the T315I cohort as compared to patients in the resistant intolerant cohort.

Nine percent of all patients had a prior stem cell transplant. Forty-one percent (185/449) of patients had prior cytotoxic chemotherapy (excludes hydroxyurea). If hydroxyurea exposure is included, 75% (335/449) had prior chemotherapy exposure.

Exposure

The median exposure duration and cumulative exposure were similar between patients with CP-CML and AP-CML, with a median exposure duration of 9 months. Patients with BP-CML and Ph+ALL had similar exposure duration and cumulative exposure, with a median exposure duration of 3 months.

**Table 32 Study 10-201 Duration of Exposure and Cumulative Exposure**

Cohort	N	Duration of Treatment, in months		Cumulative Exposure, in milligrams	
		Median	Range	Median	Range
CP-CML	270	9.2	0.1 to 16.6	8235	135 to 19485
AP-CML	85	9.4	0.5 to 18.4	7680	495 to 23220
BP-CML	62	2.9	0.03 to 14.8	3825	45 to 16605
Ph+ ALL	32	2.7	0.1 to 11.4	3578	135 to 15210

Patients from all disease cohorts were not able to maintain the treatment intensity of the starting ponatinib dose of 45 mg per day. Patients with CP-CML were only able to receive treatment at 45 mg per day dose level for 50% of the entire treatment duration, and received reduced doses of ponatinib for 36% of the treatment duration. This explains the average ponatinib daily dose of 32.1 mg for the CP-CML cohort. Similar patterns were observed in the other cohorts.

**Table 33 Study 10-201 Analysis of Treatment Intensity**

Cohort	N	Average Daily Dose, in mg	Percent of Treatment Duration at Any Dose	Percent of Treatment Duration at Full Dose
CP-CML	270	32.1	86%	50%
AP-CML	85	31.2	82%	60%
BP-CML	62	39.2	91%	71%
Ph+ ALL	32	42.3	96%	80%

Dose modifications (dose delay >2 days or dose reduction) were more common (>70%) in patients in the CP-CML and AP-CML cohorts as compared to the BP-CML (55%) and Ph+ALL (25%) cohorts.

Adverse events were the most common cause for the dose modifications. Three hundred-twenty-six patients (73%) required a dose modification due to adverse events. The most common adverse events that lead to dose modification (≥5%) were thrombocytopenia (29%), neutropenia (13%), lipase increased (11%), rash (11%), abdominal pain (10%), pancreatitis (6%), and ALT, AST, or GGT increased (6%).

**Table 34 Summary of Dose Modifications for Study 10-201**

Cohort	N	Percent with dose delay >2 days or dose reduction	Percent with dose delay >2 days	Percent with dose reduction	Percent with dose re-escalation
CP-CML	270	77%	74%	62%	14%
AP-CML	85	71%	66%	55%	11%
BP-CML	62	55%	50%	24%	6%
Ph+ ALL	32	25%	25%	13%	0%

**Table 35 Summary of Dose Reductions for Study 10-201**

	Number of patients	Median time to dose reduction, in days (95%CI)
Any dose reduction	235 (53%)	68 (58,78)
Dose reduction to 30 mg	218 (49%)	71 (59, 84)
Dose reduction to 15 mg	112 (25%)	134 (103, 148)

### 7.2.2 Explorations for Dose Response

Explorations for dose response in Study 10-201 is not possible because all patients in Study 10-201 were started at the 45 mg per day dose level.

Explorations for dose response for Study 07-101 is problematic due to the small number of patients treated overall and per dose cohort. Study 07-101 enrolled a total of 81 patients treated at the following dose cohorts: 2 mg (N=3), 4 mg (N=6), 8 mg (N=7), 15 mg (N=8), 30 mg (N=7), 45 mg (N=31), and 60 mg (N=19).

However, Study 07-101 is adequate for evaluation of the MTD (maximum tolerated dose) and DLTs (dose-limiting toxicities). According to the Study 07-101 study report:

*Pancreatic events were the most commonly occurring DLTs. Four patients treated at 60 mg daily had pancreatic related DLTs during the defined cycle 1 DLT evaluation period; these consisted of grade 3 or 4 increased lipase and/or blood amylase concurrent with clinical evidence of pancreatitis. Two patients treated at 60 mg experienced other DLTs; 1 with grade 3 fatigue; and, 1 with grade 3 alanine aminotransferase and aspartate aminotransferase increased. At 45 mg, there was 1 DLT of grade 3 rash maculo-papular. Of the 7 patients with DLTs, 3 continued study participation, 3 discontinued study treatment for reasons other than the DLT they experienced, and 1 discontinued due to the DLT.*

### 7.2.3 Special Animal and/or In Vitro Testing

Refer to the Pharmacology-Toxicology review for details.

#### 7.2.4 Routine Clinical Testing

Refer to Sections 7.4.2, 7.4.3, and 7.4.4.

Routine clinical assessments in Study 10-201 included medical history, physical exam, laboratory exams, and procedures (bone marrow evaluation, electrocardiogram, echocardiogram). Refer to Section 5.3.1.4 for detailed schedule of safety assessments.

#### 7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to Clinical Pharmacology review.

#### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The pharmacology-toxicology review noted a broad spectrum of kinase inhibition for ponatinib, which includes inhibition of the VEGFR-family of kinases. The safety profile for ponatinib is notable for similar features to kinase inhibitors active against the VEGFR-kinases. These similar features include arterial thromboembolic events, hypertension, gastrointestinal perforation, and compromised wound healing. The following listing includes FDA-approved drugs and biologics with anti-VEGF activity.

##### **Sorafenib**

- Cardiac ischemia or infarction
- Bleeding
- Hypertension
- Hand-foot skin reaction and rash
- Gastrointestinal perforation
- Temporary interruption for major surgical procedures
- QT prolongation
- Drug-induced hepatitis
- Fetal harm when administered to a pregnant woman

##### **Sunitinib**

Boxed warning: Hepatotoxicity has been observed in clinical trials and post-marketing experience. This hepatotoxicity may be severe, and deaths have been reported.
---

- Potential hazard to fetus
- Cardiac toxicity including cardiac failure and decline in left ventricular ejection fraction
- Prolonged QT interval and Torsade de Pointes
- Hypertension
- Hemorrhagic events
- Osteonecrosis of the jaw
- Tumor lysis syndrome

- Thyroid dysfunction
- Temporary interruption for major surgical procedures
- Adrenal hemorrhage in animal studies

### **Pazopanib**

Boxed warning: Severe and fatal hepatotoxicity has been observed in clinical trials. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended.

- Prolonged QT interval and Torsade de Pointes
- Cardiac dysfunction such as congestive heart failure and decreased left ventricular ejection fraction
- Fatal hemorrhagic events
- Arterial thrombotic events
- Venous thrombotic events including fatal pulmonary emboli
- Gastrointestinal perforation or fistula
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
- Hypertension including hypertensive crisis
- Interruption of therapy for surgical procedures
- Hypothyroidism
- Proteinuria
- Infection
- Fetal harm when administered to a pregnant woman

### **Axitinib**

- Hypertension
- Arterial and venous thrombotic events
- Hemorrhagic events
- Gastrointestinal perforation and fistula
- Hypothyroidism
- Interruption of therapy for at least 24 hours prior to surgery
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
- Proteinuria
- Liver enzyme elevation
- Decreased starting dose in patients with moderate hepatic impairment
- Fetal harm when administered to a pregnant woman

### **Regorafenib (Stivarga)**

Boxed warning: Severe and sometimes fatal hepatotoxicity has been observed in clinical trials. Monitor hepatic function prior to and during treatment. Interrupt and then reduce or discontinue Stivarga for hepatotoxicity as manifested by elevated liver function tests or hepatocellular necrosis, depending on severity and persistence.

- Hemorrhage
- Dermatologic toxicity

- Hypertension
- Cardiac ischemia and infarction
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
- Gastrointestinal perforation or fistula
- Wound healing complications
- Embryofetal toxicity

### **Bevacizumab (Avastin)**

Boxed warning: Gastrointestinal perforations, Surgery and Wound Healing Complications, and Hemorrhage

- Gastrointestinal Perforation: Occurs in up to 2.4% of Avastin-treated patients. Discontinue Avastin for gastrointestinal perforation.
- Surgery and Wound Healing Complications: Discontinue in patients with wound dehiscence. Discontinue at least 28 days prior to elective surgery. Do not initiate Avastin for at least 28 days after surgery and until the surgical wound is fully healed.
- Hemorrhage: Severe or fatal hemorrhage, hemoptysis, gastrointestinal bleeding, CNS hemorrhage, and vaginal bleeding are increased in Avastin-treated patients. Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis.

- Non-Gastrointestinal Fistula Formation
- Arterial Thromboembolic Events
- Hypertension
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
- Proteinuria
- Infusion Reactions
- Ovarian Failure

### **ziv-Aflibercept (Zaltrap)**

Boxed warning: Hemorrhage, Gastrointestinal perforation, Compromised Wound Healing

- Hemorrhage: Severe or sometimes fatal hemorrhage, including gastrointestinal (GI) hemorrhage, has been reported in patients who have received Zaltrap. Do not administer Zaptrap to patients with severe hemorrhage.
- Gastrointestinal perforation: Discontinue Zaltrap therapy in patients who experience GI perforation.
- Compromised Wound Healing: Discontinue Zaltrap in patients with compromised wound healing. Suspend Zaltrap for at least 4 weeks prior to elective surgery, and do not resume for at least 4 weeks following major surgery and until the surgical wound is fully healed.

- Fistula Formation
- Hypertension
- Arterial Thromboembolic Events
- Proteinuria

- Neutropenia and Neutropenic Complications
- Diarrhea and Dehydration
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

### 7.3 Major Safety Results

**Table 36 Safety Summary for Study 10-201**

Event	N	%
Deaths	57	13%
Progressive Disease	29	6%
Adverse Event	28	6%
Serious TEAE*	217	48%
Discontinuations due to TEAE*	67	15%
Any Grade 3 to 4 TEAE*	354	79%
Any TEAE*	446	99%

\*Excludes terms related to progressive disease

#### 7.3.1 Deaths

Fifty-seven patients (13%) died during the study or within 30 days after treatment discontinuation. The causes of death were progressive disease (29 patients) or adverse event (28 patients). Deaths due to adverse events are shown in Table 37.

The most common cause of death due adverse event were due to infections (10 deaths total: 3 from septic shock, 2 from sepsis, 4 from pneumonia, and 1 from infectious colitis). An additional 2 deaths coded as multi-organ failure (SUBJID 001-001 and 001-004) had concurrent diagnoses of Klebsiella sepsis and septic shock, respectively at the time of death.

**Table 37 Deaths on Study or Within 30 Days after Discontinuation, Excluding Progressive Disease: Study 10-201**

MedDRA Preferred Term	Cohort	SUBJID	Days on Study
<b>Infections</b>			(b) (6)
SEPTIC SHOCK	Ph+ ALL	129-002	
SEPTIC SHOCK	CML - AP	701-007	
SEPTIC SHOCK	Ph+ ALL	961-002	
SEPSIS	CML - BP	040-007	
SEPSIS	CML - BP	127-002	
PNEUMONIA	CML - CP	011-008	
PNEUMONIA	CML - CP	947-003	
PNEUMONIA FUNGAL	CML - AP	938-002	
PNEUMOCYSTIS JIROVECI PNEUMONIA	CML - CP	962-010	

MedDRA Preferred Term	Cohort	SUBJID	Days on Study
ENTEROCOLITIS INFECTIOUS	CML - BP	129-001	(b) (6)
<b>Cardiac Disorders</b>			
ACUTE MYOCARDIAL INFARCTION	CML - CP	967-008	
CARDIAC FAILURE	CML - BP	011-002	
CARDIAC FAILURE CONGESTIVE	CML - CP	034-001	
CARDIAC FAILURE CONGESTIVE	CML - BP	961-003	
CARDIOPULMONARY FAILURE	Ph+ ALL	959-008	
CARDIAC ARREST	Ph+ ALL	083-008	
CARDIAC ARREST	CML - CP	938-024	
CARDIAC ARREST	CML - CP	941-003	
<b>Nervous System</b>			
HAEMORRHAGE INTRACRANIAL	CML - BP	011-006	
HAEMORRHAGE INTRACRANIAL	CML - BP	965-003	
HAEMORRHAGIC CEREBRAL INFARCTION	CML - CP	938-017	
ISCHAEMIA	Ph+ ALL	956-002	
SUBDURAL HAEMATOMA	CML - CP	058-002	
<b>General Disorders</b>			
MULTI-ORGAN FAILURE	CML - BP	001-001	
MULTI-ORGAN FAILURE	CML - BP	001-004	
PYREXIA	CML - AP	785-001	
<b>Gastrointestinal Disorders</b>			
GASTRITIS HAEMORRHAGIC	CML - BP	017-003	
<b>Metabolism and Nutrition</b>			
DEHYDRATION	CML - BP	005-028	

Hemorrhagic events were the next most common cause for death (4 deaths due to CNS hemorrhage and 1 death due to hemorrhagic gastritis). The platelet count at the time of the hemorrhagic event was low in 4 of the patients (nadir platelet counts between 6 to 40 x 10<sup>9</sup>/L), and unknown in patient 938-017. Three patients with fatal CNS hemorrhage were not on study treatment at the time of onset of the fatal event. One patient (011-006) experienced fatal intracranial hemorrhage (b) (6) after discontinuing study treatment. Patient 011-006 had a platelet count of 11 x 10<sup>9</sup>/L on the day of the fatal CNS hemorrhage.

Three patients died due to cardiac failure. Two of the patients were on study treatment at the time of onset of fatal cardiac failure. Patient 011-002 was not on study treatment at the time of onset of fatal cardiac failure, but was on study treatment at the initial diagnosis of cardiac failure (EF of 25%-35% from prior baseline EF of 45%).

Ischemic events leading to death occurred in 2 patients. Patient 967-008 experienced fatal acute myocardial infarction while on study treatment. Patient 956-002 experienced fatal cerebral and limb ischemia (b) (6) after discontinuing study treatment..

Review of narratives did not identify the likely cause of death in 5 patients (3 patients with cardiac arrest, 1 with cardiopulmonary failure, 1 with pyrexia). Three of the deaths

occurred out-of-hospital (pyrexia, 2 cardiac arrests) and detailed information was not available regarding events surrounding the time of death. Two of the deaths occurred during hospitalization (patient 941-003 and 959-008). Both patients were admitted for treatment of infectious conditions (lobar pneumonia and invasive aspergillosis, respectively) when patients subsequently died due to cardiac arrest or cardiopulmonary failure. In the narrative for patient 941-003, the investigator reported that a ventricular tachyarrhythmia with an increased QT wave could not be excluded as a precipitant for the fatal cardiac arrest.

One patient (005-028) died due to dehydration. Patient had presented with diarrhea, decreased appetite, and hypotension. During the hospitalization, patient was placed on palliative measures, and subsequently died.

### 7.3.2 Nonfatal Serious Adverse Events

**Table 38 Treatment-Emergent Serious Adverse Events in  $\geq$  2% of Patients in Study 10-201**

<b>Treatment-Emergent Serious Adverse Event (SAE)</b>	<b>N (%)</b>
<b>Cardiovascular disorders</b>	
Arterial ischemic event	27 (6%)
Myocardial infarction or worsening coronary artery disease	18 (4%)
Stroke or TIA	7 (2%)
Peripheral arterial disease	4 (1%)
Hemorrhage	19 (4%)
CNS hemorrhage	10 (2%)
Gastrointestinal hemorrhage	6 (1%)
Cardiac failure	17 (4%)
Effusions*	10 (2%)
Atrial fibrillation	9 (2%)
Hypertension	8 (2%)
Venous thromboembolism	8 (2%)
<b>Gastrointestinal disorders</b>	
Pancreatitis	23 (5%)
Abdominal pain	16 (4%)
<b>Blood and lymphatic system disorders</b>	
Febrile neutropenia	13 (3%)
Thrombocytopenia	12 (2%)
Anemia	12 (2%)
<b>Infections</b>	
Pneumonia	21 (5%)
Sepsis	10 (2%)
<b>General</b>	
Pyrexia	14 (3%)

\*includes pericardial effusion, pleural effusion, and ascites

Refer to Section 7.3.4 for details of the serious adverse events presented in an issue-based format.

### 7.3.3 Dropouts and/or Discontinuations

Discontinuations due to adverse events occurred in 15% of the patients. The most common adverse events that lead to treatment discontinuation include thrombocytopenia (18 patients), sepsis or systemic inflammatory response syndrome (6 patients), cardiac failure (5 patients), pneumonia (4 patients), hemorrhage (4 patients), and CNS or cardiac ischemia (3 patients). The rates of treatment-related adverse events resulting in discontinuation were 13% in CP-CML, 12% in AP-CML, 24% in BP-CML, and 19% Ph+ALL

### 7.3.4 Significant Adverse Events

#### 7.3.4.1 Arterial Ischemic Events (arterial thromboembolism and arterial stenosis)

Arterial thromboembolic and arterial stenosis events occurred in patients on ponatinib treatment in Study 10-201 and consisted of cardiac, central nervous system, and peripheral arterial events. As of the original data cutoff (27 April 2012), 41 patients (9%) of all patients in Study 10-201 experienced an arterial event, of which 27 patients experienced a serious ischemic event. The 120-day safety update (data cutoff 23 July 2012) showed an increase number of arterial events: 51 patients (11%) with any grade event and 34 patients experienced a serious ischemic event.

**Arterial Ischemic Events.** Myocardial ischemia or worsening coronary artery disease were the most common arterial occlusive or thromboembolic event, and occurred as a serious event in 21 patients (updated data cutoff 7/23/12). Sixteen patients (76%) required a revascularization procedure (PTCA, CABG, or both). Eleven of the patients (52%) developed congestive heart failure concurrent or subsequent to the myocardial ischemic event. Fourteen patients experienced acute myocardial infarction.

Eight patients experienced a serious ischemic CNS event. Two of the patients experienced hemorrhagic conversion of the initial ischemic event.

Seven patients experienced a serious peripheral arterial ischemic event. Four patients required peripheral arterial PTCA or bypass surgery. Three patients developed digital or distal extremity necrosis; and 2 of these 3 patients required amputations.

The median time to develop any serious ischemic event was 5.8 months. Serious myocardial and CNS ischemic events occurred earlier (median TTE of 5.3 and 5.7 months) compared to peripheral arterial events (median TTE of 6.7 months).

**Arterial Stenosis.** Arterial stenosis was documented in 24 patients (5% of all patients, 71% of patients with serious ischemic event). Twenty-one patients required a revascularization procedure (16 patients with coronary revascularization, 4 patients with peripheral arterial revascularization, and 1 patient with cerebrovascular revascularization).

Arterial stenosis in major arteries that supply the central nervous system occurred in four patients. The locations of cerebrovascular arterial stenosis include: bilateral MCA (1 patient); R ICA, R vertebral and basilar (1 patient); carotid artery supraclinoid (1); vertebral and subclavian artery (1 patient).

The clinical course of patient 127-003 was notable for progressive coronary artery stenosis. Patient 127-003 is a 66 year old male with CP-CML who was deemed ineligible for a HSCT due to positive results on a pre-transplant stress echocardiogram. Patient was then enrolled to Study 10-201.

- Patient underwent coronary angiography (b) (6) prior to starting ponatinib treatment and had the following findings: luminal irregularities L Main, 30% stenosis LAD, RCA diffuse luminal irregularities. Due to the anatomical findings and absence of symptoms, the recommendation for treatment was aggressive medical therapy. Treatment was initiated with ASA 81 mg, simvastatin 40 mg, metoprolol XL 25 mg, and ramipril 2.5 mg daily.
- On D (b) (6), patient underwent repeat coronary angiography for new-onset exertional angina. The L main coronary artery showed diffuse disease with at least 50% stenosis (compared to luminal irregularities on D (b) (6)). The proximal LAD showed disease and an increase to 50 to 60% stenosis, increased from 30% on D (b) (6). The RCA had eccentric 60 to 70% stenosis. The post-procedure recommendation included continued medical therapy and likely coronary bypass surgery. Reassessment of the investigational therapy was done to consider the possibility that the regimen was

*“contributing to the unusual, rapidly progressive atherosclerotic process.”*

- The investigator provided considerations regarding his assessment of the event's possible relationship to the study drug. He reported that according to the cardiologist, there was unparalleled progression of CAD found during the D (b) (6) angiogram as compared to the baseline evaluation of CAD completed on 5 months prior. Additionally, the patient had a minor scaly rash on the skin just behind his axillae bilaterally and some scaly thickening on his hands. He also reported having a slightly hoarse voice. The investigator reported that the skin changes and hoarse voice could suggest a proliferative response paralleled by a

proliferative response in the epithelium of his coronary arteries. He concluded that there might be a plausible connection to the study drug, and as a result, ponatinib treatment was permanently discontinued on D (b) (6).

**Recurrent or Multiple-Site Ischemic Events.** Recurrent or multiple-site arterial occlusive or thromboembolic events occurred in 13 patients. Examples of the patient histories with recurrent arterial events include:

- Patient 938-017: 69 year old male with CP-CML with history of diabetes and hypertension, but on no medications for diabetes or hypertension. On D (b) (6), patient experienced L hand weakness, L hemifacial paresthesia, and diplopia. MRA showed multifocal stenosis of distal R ICA. Doppler studies showed stenosis R ACA, distal basilar artery, L prox ICA, and near-occlusion of prox R vert artery. On D (b) (6) patient experienced L leg weakness and was diagnosed with cerebral infarction. Patient underwent PTCA. On D (b) (6), patient experienced L-sided weakness and dysarthria; diagnosis was cerebral infarction. Patient underwent superficial temporal artery to middle cerebral artery anastomosis. On D (b) (6), patient experienced of hemorrhagic CVA and died on D (b) (6).
- Patient 701-017: 70 year old male with AP-CML with history of diabetes, insulin-requiring since 1997. On D (b) (6) patient experienced L foot necrosis and underwent PTCA of the L fibular artery. On D (b) (6) patient experienced necrosis of the second digit of L foot and was diagnosed with L post tibial artery occlusion and patient underwent digital amputation. On D (b) (6), patient underwent repeat PTCA of L fibular artery.
- Patient 005-002: 38 year old female with CP-CML and PMHx of diabetes (treated with glipizide since 2009 and metformin since 2011) and rheumatoid arthritis (treated with Arava) presented on D (b) (6) with severe difficulty of using R hand. MRI showed L hemispheric acute stroke, and CT studies were suspicious for stenosis and/or partial occlusion of L ICA (supraclinoid). On D (b) (6), patient presented with R hand numbness and speech difficulty. MRI and CT showed acute stroke.
- Patient 953-001: 54 year old male with no history of hypertension, diabetes, or hyperlipidemia, was documented to have myocardial infarction on D (b) (6) during scheduled echocardiography. On D (b) (6) patient presented with a serious adverse event of congestive heart failure, and patient required PTCA of LAD.
- Patient 947-004: 67 year old male with AP-CML with history of hypertension and L ventricular hypertrophy presented on D (b) (6) with acute MI and underwent coronary artery bypass surgery. On D (b) (6), patient experienced bilateral cerebellar infarction and was documented to have subclavian artery stenosis and vertebral artery stenosis.

**Table 39 Univariate Analysis of Baseline Factors Associated with Arterial Ischemic Events**

Baseline Parameter	Subgroup	N	AE (%)	P-value <sup>1</sup>	SAE (%)	P-value <sup>1</sup>
Overall	None	449	11.4		7.6	
Gender	Male	238	12.2	0.655	9.2	0.211
	Female	211	10.4		5.7	
<b>Age (years)</b>	<b>&lt;50</b>	<b>145</b>	<b>2.1</b>	<b>&lt;0.001</b>	<b>2.1</b>	<b>0.001</b>
	<b>50 to 65</b>	<b>161</b>	<b>14.9</b>		<b>8.1</b>	
	<b>66 to 74</b>	<b>105</b>	<b>12.4</b>		<b>11.4</b>	
	<b>≥ 75</b>	<b>38</b>	<b>28.9</b>		<b>15.8</b>	
BMI (kg/m <sup>2</sup> )	<25	187	11.8	0.922	7.0	0.680
	25 to <30	154	10.4		9.1	
	≥30	107	11.2		6.5	
Race	Caucasian	352	11.3	1.000	7.7	1.000
	Non-Caucasian	97	11.3		7.2	
Diagnosis	CP-CML	270	13.0	0.317	8.1	0.551
	AP-CML	85	11.8		9.4	
	BP-CML	62	8.1		4.8	
	Ph+ ALL	32	3.1		3.1	
T315l (b) (4)	Yes	128	13.3	0.414	8.6	0.693
	No	321	10.6		7.2	
Number of Prior TKIs <sup>2</sup>	1 to 2	200	10.5	0.655	8.0	0.858
	3+	249	12.0		7.2	
Prior HSCT	Yes	40	7.5	0.602	7.5	1.000
	No	409	11.7		7.6	
Prior chemotherapy <sup>3</sup> (excluding hydroxyurea)	Yes	185	10.8	0.880	8.1	0.721
	No	264	11.7		7.2	
Prior chemotherapy <sup>3</sup> (including hydroxyurea)	Yes	335	11.9	0.609	8.6	0.156
	No	114	9.6		4.4	
<b>Time from first diagnosis (years)</b>	<b>&lt;5</b>	<b>197</b>	<b>6.6</b>	<b>&lt;0.001</b>	<b>4.6</b>	<b>0.012</b>
	<b>5 to &lt;10</b>	<b>114</b>	<b>7.9</b>		<b>6.1</b>	
	<b>≥ 10</b>	<b>138</b>	<b>21.0</b>		<b>13.0</b>	
<b>Prior arterial ischemia or any vascular procedure<sup>4</sup></b>	<b>Yes</b>	<b>59</b>	<b>35.6</b>	<b>&lt;0.001</b>	<b>27.1</b>	<b>&lt;0.001</b>
	<b>No</b>	<b>390</b>	<b>7.7</b>		<b>4.6</b>	
<b>Diabetes<sup>4</sup></b>	<b>Yes</b>	<b>56</b>	<b>32.1</b>	<b>&lt;0.001</b>	<b>25.0</b>	<b>&lt;0.001</b>
	<b>No</b>	<b>393</b>	<b>8.4</b>		<b>5.1</b>	
<b>Hypertension</b>	<b>Yes</b>	<b>158</b>	<b>17.7</b>	<b>0.002</b>	<b>12.7</b>	<b>0.003</b>
	<b>No</b>	<b>291</b>	<b>7.9</b>		<b>4.8</b>	
Dyslipidemia	Yes	91	16.5	0.084	11.0	0.183
	No	358	10.1		6.7	

**Notes:** (1) P-values shown are exact 2-sided P-values for parameters with 2 subgroups, and chi-square P-values for parameters with  $\geq 3$  subgroups.

(2) TKIs included in analysis: imatinib, dasatinib, nilotinib, bosutinib

(3) Most common chemotherapy exposure ( $\geq 2\%$ ): hydroxyurea (56%), cytarabine (27%), cyclophosphamide (9%), omacetaxine (9%), vincristine (7%), methotrexate (7%), busulfan (5%), doxorubicin (5%), dexamethasone (4%), daunorubicin (4%), fludarabine (4%), idarubicin (4%), mercaptopurine (4%), prednisone (3%), asparaginase (3%), etoposide (3%)

(4) Seventeen patients had diabetes and prior arterial ischemia. The AE and SAE risk for this subpopulation were 47% and 41% respectively.

**Table 40 Multivariate Logistic Regression Analysis for Serious Arterial Ischemic Events**

Parameter (Starting Model)	Estimate	Standard Error	P value
Gender	-0.3448	0.4304	0.4231
<b>Age</b>	<b>0.633</b>	<b>0.239</b>	<b>0.0081</b>
Body Mass Index	-0.1909	0.2821	0.4987
Race	0.3437	0.5187	0.5076
Diagnosis	-0.1336	0.2706	0.6215
T315I (b) (4)	0.169	0.4773	0.7233
Number of prior TKI	-0.5853	0.4279	0.1713
Prior HSCT	0.2778	0.8128	0.7325
Prior chemotherapy (excludes hydroxyurea)	0.1289	0.4825	0.7893
Time from first diagnosis	0.4055	0.2799	0.1474
<b>Prior arterial ischemia</b>	<b>1.6217</b>	<b>0.4604</b>	<b>0.0004</b>
<b>Diabetes</b>	<b>1.6158</b>	<b>0.4677</b>	<b>0.0006</b>
Hypertension	0.2532	0.4853	0.6019
Dyslipidemia	-0.504	0.5231	0.3353
Parameter (Final Model)	Estimate	Standard Error	P value
<b>Age</b>	<b>0.6099</b>	<b>0.2152</b>	<b>0.0046</b>
<b>Prior arterial ischemia</b>	<b>1.5818</b>	<b>0.4018</b>	<b>&lt;0.0001</b>
<b>Diabetes</b>	<b>1.6276</b>	<b>0.4188</b>	<b>0.0001</b>
Intercept	-4.7164	0.6238	<0.0001

**Risk Factor Analysis for Ischemic Events.** Univariate analysis of baseline factors associated with any grade or serious arterial occlusive or thromboembolic events showed a significant ( $P < 0.01$ ) association with age, time from first diagnosis, prior arterial ischemia or any vascular procedure, diabetes, and hypertension (refer to Table 39). Multivariate logistic regression analysis for serious arterial events showed an

association for age, prior arterial ischemia or vascular procedure, and diabetes (refer to Table 40).

**Table 41 Actual SAE Risk for Arterial Ischemic Event in Study 10-201**

<b>Age Group</b>	<b>No prior ischemic and non-diabetic</b>	<b>Prior ischemia, diabetes, or both</b>
Less than 50	<b>0.8%</b> (1/131)	<b>14.3%</b> (2/14)
50 to 65	<b>1.7%</b> (2/115)	<b>23.9%</b> (11/46)
66 to 74	<b>6.4%</b> (5/78)	<b>25.9%</b> (7/27)
75 and older	<b>11.1%</b> (3/27)	<b>27.3%</b> (3/11)

**Note:** The overall SAE risk is 7.6% (34/449) in patients with a median duration of exposure of 12 months.

The actual SAE arterial ischemic risk is shown in Table 41, and demonstrates an increased ischemic risk with increasing age. Concomitant history of diabetes or prior arterial ischemic event further worsens the risk for arterial ischemia.

**Arterial Ischemic Events in Study 07-101 and Expanded Access Program.** Arterial occlusive or thromboembolic events also occurred in patients in Study 07-101. As of the data cutoff date of 23 July 2012, 18 of 81 patients (22%) in Study 07-101 experienced an arterial event of whom 12 patients (15%) experienced a serious event.

Subset analysis of patients with CP-CML or AP-CML treated at the following dose levels 15 mg, 30 mg, 45 mg, and 60 mg showed arterial ischemic events occurred at all dose levels. The overall serious ischemic risk in this subset was 18% (9/49), and corresponded to a median duration of exposure of 26 months.

**Table 42 Arterial Ischemic Events in Patients with CP-CML or AP-CML in Study 07-101**

<b>Final Dose Level</b>	<b>N</b>	<b>Any grade ischemic event</b>	<b>Serious ischemic event</b>
15 mg	5	2 (40%)	2 (40%)
30 mg	8	2 (25%)	1 (13%)
45 mg	22	4 (18%)	2 (9%)
60 mg	14	4 (29%)	4 (29%)

The following cases illustrate the arterial ischemic events that have been reported in the expanded access program and named patient program for ponatinib:

- Patient DE000833: 53 year old male patient with CP-CML and unknown past medical history presented on D (b) (6) with loss of vision. MRI showed infarction of bilateral posterior cerebral arteries and several high grade stenosis of basal cerebral arteries. Patient died on D (b) (6).
- Patient IT000715: 59 year old male with CP-CML and past medical history of hypertension, COPD, presented on D (b) (6) with acute MI. Clinical course was complicated by acute respiratory failure, pulmonary edema, and persistent episodes of non-sustained ventricular tachycardia.
- Patient US000837: 77 year old female with CP-CML and past medical history of coronary artery disease s/p multiple vessel stents, peripheral artery disease, bilateral iliac artery stents, renal artery stents presented on D (b) (6) with chest pain and worsened hypertension. Patient was found to have in-stent thrombosis on cardiac catheterization, and required placement of 4 additional coronary stents.
- Patient GB000678: 58 year old male with CML developed Grade 4 acute myocardial infarction.
- Patient DE000185 71 year old female with ALL developed Grade 2 transient ischemic attack.

**Labeling Recommendation:** Box warning is recommended for arterial thromboembolic events and arterial stenosis due to the clinical severity of the events and potential for additional morbidity risk (including fatalities) with longer-term follow-up. Arterial ischemic events and arterial stenosis were observed in Study 10-201, 07-101, and in the expanded access program.

**Reviewer Comment (1):** Given the safety signal for recurrent ischemic events observed during ponatinib treatment, re-evaluation of benefit-risk should be done at the initial ischemic event. For patients with alternative treatment options, ponatinib discontinuation is recommended.

**Reviewer Comment (2):** Possible mechanisms of action for the arterial ischemic events and arterial stenosis include the broad spectrum of kinase inhibition, VEGFR-kinase inhibition, and insolubility of ponatinib in aqueous solutions. Ponatinib was designed to target native and mutated bcr-abl, however, in vitro testing revealed a broader spectrum of kinase inhibition, which included the VEGFR-family of kinases. Arterial ischemic events have been associated with kinase inhibitors that target VEGFR (refer to USPI for

sorafenib, pazopanib, axitinib, and regorafenib). Also, the occurrence of other adverse events typically more associated with pan-kinase inhibition or VEGFR-kinase inhibition such as hypertension, proteinuria, oral mucositis, and gastrointestinal perforation, further supports the above hypothesis. Hypertension, arterial ischemic events, proteinuria, and gastrointestinal perforation have also been observed in drugs with VEGF-specific inhibition (i.e. bevacizumab and ziv-aflibercept). However, the relative contribution of VEGFR-kinase inhibition cannot be determined. Another possible explanation may be the relative insolubility of ponatinib in aqueous solutions (Refer to Section 4.1 and Table 2). This insolubility may lead to precipitation of ponatinib in the circulation and subsequent deposition in areas of turbulent flow such as in the arterial system.

#### 7.3.4.2 Hepatic toxicity

Ponatinib treatment is associated with hepatic toxicity, which may range from fulminant hepatic failure to asymptomatic hepatic transaminase elevation.

One case of fulminant hepatic failure occurred in the Applicant's clinical trial in Japan (AP24534-11-106). The patient (JP000795) was a 64 year old female with Ph+ ALL s/p unrelated BMT in 2004. The summary of patient's clinical course is provided in Figure 5. The baseline liver function tests were within normal limits at time of study entry.

*Briefly, patient started ponatinib treatment at a dose of 30 mg/day on C<sup>(b) (6)</sup>. On C<sup>(b) (6)</sup>, patient complained of feeling tired. On C<sup>(b) (6)</sup>, patient complained of feeling slightly drowsy, light-headed and a "floating feeling". On C<sup>(b) (6)</sup>, patient was unsteady on her feet and her speech became unclear. Laboratory findings were notable for markedly elevated AST (approximately 145 x upper limit of normal [ULN]) and ALT (approximately 65 x ULN). The patient was considered to have hepatic failure with encephalopathy and renal impairment. Head CT did not show intracranial hemorrhage. Steroid pulse therapy (methylprednisolone) 1000 mg QDay was started. The patient also underwent plasma exchange and hemodiafiltration. On C<sup>(b) (6)</sup>, the patient's AST increased to as high as 246 x ULN and ALT as high as 83 x ULN; total bilirubin was 3 x ULN, with peak alkaline phosphatase values less than 1.2 x ULN. Work-up for hepatic viral infections were negative. The patient's clinical course was also complicated by disseminated intravascular coagulation (platelet count  $48 \times 10^9/L$ , fibrinogen 90 mg/dL, subcutaneous bleeding in inguinal area and thigh). On C<sup>(b) (6)</sup>, patient became progressively hypotensive despite maximal vasopressor support. Patient subsequently died, and the investigator reported the cause of death as drug-induced fulminant hepatitis. Needle-biopsy of the liver was performed post-mortem, and results showed hepatocellular necrosis with severe adipose degeneration.*

**Figure 5 Case Summary: Fulminant Hepatic Failure**

Hx: 64/F with Ph+ALL s/p BMT 8 yrs prior	Day	Ponatinib Dose	ALT (IU/L, 4-34)	AST (IU/L, 7-38)	Bilirubin (mg/dL, 0.2-1.2)	Alk Phos (U/L,103-335)	Other Labs
	(b) (6)		13	21	0.4	141	INR 1.1
		30 mg	22	30	0.4	162	
feeling tired →		30 mg					
slightly drowsy and light-headed →		30 mg					
general weakness, unclear speech →			2477	5505	2.0	391	LDH 10883 INR 3.2
Dx: hepatic encephalopathy GCS 13 → 10			3053	9358	3.1		
			2327	5778	3.3	313	LDH 5879 INR 2.4
			874	1581		332	LDH 1328
			557	900		353	LDH 723
patient died on D10 →			380	638		361	LDH 668

Other: negative hepatitis serologies; head CT no hemorrhage; liver US no masses or obstruction

**Investigator assessed cause of death: fulminant hepatic failure**  
Liver needle biopsy: hepatocellular necrosis with severe adipose degeneration

**Reviewer Comment:** The contribution of ponatinib in the above case of fulminant hepatic failure cannot be ruled out. The absence of inflammatory infiltrate on the post-mortem liver biopsy lead to a pathologic diagnosis of shock liver. However, this may be confounded by the use of high-dose corticosteroids and other immunomodulating procedures such as plasma exchange that were administered to the patient. Also, the clinical course was notable for persistent hypotension despite maximal vasopressor support, hence the post-mortem biopsy findings consistent with shock liver are not unexpected. The clinical team agrees with the investigator assessment that the drug-induced fulminant hepatitis is consistent with the clinical course observed in above patient (JP000795).

Two additional cases of acute hepatic failure or acute liver injury were reported in patients on ponatinib treatment. Both cases were associated in the setting of neoplasm progression. One case was a patient in Study 10-201 (Patient 027-022). The second case was a patient from the expanded access program.

Hepatic toxicity with ponatinib may also manifest as hepatic transaminase elevations. The incidence of any ALT or AST elevation was 55% (all grades) and 8% (grade 3 or 4). Transaminase elevation was not reversible in 7% of patients who experienced ALT or AST elevation. The median time to onset of ALT or AST elevation was 46 days (range 1 to 334 days). The median duration of ALT or AST elevation was 29 days.

**Labeling Recommendation:** Box warning is recommended for hepatic toxicity given the cases of fatal acute hepatic failure and the frequency of hepatic transaminase elevation.

### 7.3.4.3 Myelosuppression

Ponatinib treatment is associated with severe (NCI CTC grade 3 or 4) thrombocytopenia, neutropenia, and anemia (refer to Table 42 and Table 46). The frequency of these events is greater in patients with BP-CML and Ph+ALL followed by AP-CML, then patients with CP-CML. Similarly, febrile neutropenia was more common in patients with BP-CML and Ph+ALL than in patients with AP-CML or CP-CML. The use of supportive hematologic care measures such as transfusions or G-CSF support in Study 10-201 was also more common in patients with more advanced disease (refer to Table 43).

The median time to onset for treatment-emergent thrombocytopenia or neutropenia were 22 days and 29 days, respectively. Treatment-emergent thrombocytopenia or neutropenia occurred throughout the duration of treatment.

**Table 43 Summary of Myelosuppression-Related Events**

	<b>CP-CML</b> N=270 (%)	<b>AP-CML</b> N=85 (%)	<b>BP-CML</b> N=62 (%)	<b>Ph+ ALL</b> N=32 (%)
Grade 3 or 4 Cytopenia				
Thrombocytopenia	34	47	44	47
Neutropenia	23	47	48	59
Anemia	9	24	52	41
Febrile Neutropenia	1	4	11	25
Transfusions during study				
Platelets	16	36	77	72
Packed RBCs	14	44	89	75
Received granulocyte-stimulating colony factors during study	8	19	23	34

Dose modification due to myelosuppression was common. Thrombocytopenia resulted in dose modification in 29% of the patients. Neutropenia resulted in dose modification in 13% of the patients. Most of the dose modifications for myelosuppression consisted of dose interruptions rather than dose reductions.

**Labeling Recommendation:** The Applicant's proposed dose modifications for myelosuppression in the label are acceptable and are consistent with other drugs in this class.

**Infections.** Treatment-emergent infections occurred in 50% of the patients. The most common infections were upper respiratory tract infection, nasopharyngitis, urinary tract infection, pneumonia, and sinusitis. Treatment-emergent serious infections were reported in 15% of the patients. The most common serious infections were pneumonia, sepsis, and cellulitis.

**Reviewer Comment:** Myelosuppression and infection TEAEs are not unexpected in patients with CML or Ph+ALL treated with tyrosine kinase inhibitors. Refer to Section 7.3.4.4 regarding hemorrhages.

#### 7.3.4.4 Hemorrhages

Hemorrhagic events occurred in 23% of the patients in Study 10-201. Serious hemorrhagic events occurred in 19 patients (4%). The most common sites of serious hemorrhage were CNS (10 patients) and gastrointestinal (6 patients).

Most hemorrhagic events were associated with severe thrombocytopenia. However, serious hemorrhages were also reported in patients with mild thrombocytopenia (platelet count  $\geq 100 \times 10^9/L$ ).

**Reviewer Comment:** Although the predominant mechanism for hemorrhage was severe thrombocytopenia, the occurrence of serious bleeding events in patients with platelet counts  $\geq 100 \times 10^9/L$  suggests a functional platelet defect, which may be similar to that described with dasatinib. The application did not contain information regarding in vitro platelet function assays. However, Neelakantan et al published a brief report regarding 5 patients who received ponatinib therapy who were documented to have prolonged closure times on PFA100 testing.

#### 7.3.4.5 Pancreatic Events

Ponatinib treatment is associated with pancreatic events. In Study 10-201, the incidence of clinical pancreatitis was 6%. The incidence of lipase elevation was 31%.<sup>1</sup> The median time to onset of clinical pancreatitis was 13 days (range 3 to 246 days) and had a median duration of 7 days. The median time to onset for lipase elevation was 25 days (range 1 to 344 days) and had a median duration of 15 days<sup>2</sup>. In Study 07-101,

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<sup>1</sup> The number of patients with treatment-emergent lipase evaluation was determined based on review of the following sources: AE dataset, LB dataset, and narratives for pancreatitis. Two patients who experienced a pancreatic event did not have lipase elevation: patient 040-003 had normal lipase levels throughout an episode of US-confirmed pancreatitis; patient 797-001 did not have lipase levels documented during an event characterized by L upper quadrant pain and CT-confirmed pancreatic inflammation.

<sup>2</sup> Based on AE data only; lab data not reliable for duration because not all of unscheduled labs were captured.

pancreatic events were the most common dose-limiting toxicity with 4 cases observed at the 60 mg dose level.

Twenty-three patients had pancreatitis as an SAE. This was primarily due to hospitalization of the patients with pancreatitis. In-hospital management consisted of bowel rest and supportive care (IV hydration, management of pain and other symptoms such as nausea or vomiting). There were no deaths due to pancreatitis. None of the patients who developed pancreatitis required surgical intervention.

Pancreatic events were generally reversible. Only one out of the 28 patients who developed pancreatitis did not have resolution of pancreatitis; that patient (SUBJID 938-021) died of disease progression (increased circulating blasts) prior to resolution of pancreatitis.

Pancreatic events lead to dose modifications (reductions or delays) in 51 patients (11%) for elevated lipase elevation and 25 patients (6%) for clinical pancreatitis. In cases of dose interruptions due to symptomatic pancreatitis, ponatinib retreatment was generally not restarted until resolution of pancreatitis and lipase elevation. In one patient, (SUBJID 005-006), ponatinib was restarted after resolution of symptoms, however patient still had elevated lipase. Serum lipase increased again after 1 day and patient required further treatment interruption.

**Labeling Recommendation:** Warnings and precautions section should be revised to provide more granular data regarding clinical course for pancreatitis and lipase elevation. Dose modification criteria should be modified to reflect actual practice observed in the clinical trial.

**Reviewer Comment (1):** Additional analysis using SMQ 13.0 algorithm method for acute pancreatitis was performed. Twenty-five patients who were classified as having “lipase elevation only” met the following SMQ criteria for pancreatitis: lipase elevation associated with a concurrent symptom (i.e., abdominal distention, abdominal pain, nausea, vomiting). A standard definition for pancreatitis for future or ongoing clinical trials with ponatinib would be helpful in further characterization of pancreatic events.

**Reviewer Comment (2):** Pancreatic events, mainly elevated lipase, have also been reported with imatinib, dasatinib, or nilotinib. The USPI for nilotinib includes lipase elevation in the Warnings and Precautions section.

#### 7.3.4.6 Hypertension

Treatment-emergent hypertension occurred in patients treated with ponatinib. From the VS dataset, the incidence of treatment-emergent hypertension (defined as SBP  $\geq$  140 mm Hg or DBP  $\geq$  90 mm Hg) was 71% (319/449 patients). The incidence of treatment-emergent Stage 2 hypertension (defined as SBP  $\geq$  160 mm Hg or DBP  $\geq$  100 mm Hg)

was 37% (168/449 patients). However, from the AE dataset, only 81 patients (18%) were reported with treatment-emergent hypertension.

**Reviewer Comment (1):** The discordance in the incidence of treatment-emergent HTN between VS and AE datasets may reflect under-reporting of hypertension by the investigators, specifically of cases of Stage 1 hypertension (SBP  $\geq$  140 mm Hg but  $<$ 160 mm Hg, or DBP  $\geq$  90 mm Hg but  $<$  100 mm Hg).

Eight patients (2%) experienced hypertension as a serious adverse event, and required urgent clinical intervention (refer to Table 44). Three of the 8 patients did not have a prior history of hypertension. The 5 patients with prior history of hypertension were not on anti-hypertensive medication treatment at the time of study entry.

**Table 44 Study 10-201 Hypertension Serious Adverse Event**

SUBJID	Prior H/O HTN	Baseline BP	BP at time of SAE	Comment
007017	Yes	117/57	240/105	82/F, presented with confusional state, required ER visit and hospitalization
008009	Yes	126/68	226/91	63/F, presented with headaches and flushing, required urgent care visit
023001	Yes	148/70	200/100	73/F, presented with HTN and headache, required hospitalization
027015	Yes	148/79	181/102	61/F, presented with shortness of breath, required hospitalization
048004	No	130/78	190/90	66/M, presented with chest pain, required hospitalization
701014	No	120/75	not provided	62/F, experienced hypertensive crisis (headache, somnolence, weakness on R half of body) while hospitalized for neoplasm progression, CT showed cerebral hemorrhage in occipital region
961012	No	110/80	170/115	38/M, required multiple anti-hypertensive medications, and had sequelae of chronic hypertension
962009	Yes	140/70	190/100	71/M, presented with headache, 3-day history of vertigo, diffuse abdominal pain, and acute respiratory insufficiency associated with hypertension (BP 190/100), required ER visit and hospitalization

The median time-to-onset for any grade hypertension was 29 days. The median time-to-onset for Stage 2 hypertension ( $\geq$  CTCAE Grade 3) was 55 days.

Based on the MH dataset, 158 patients (35%) had a diagnosis of hypertension at baseline. Forty-five patients (10% of all patients, 28% of 158 patients with baseline HTN) were on concomitant anti-hypertensive medications. During the study treatment, 125 patients (28%) in Study 10-201 required initiation of new anti-hypertensive treatment, of which 66 patients required more than one class of anti-hypertensive medication. The median time-to-onset of new or additional anti-hypertensive medication was 80 days. At the last visit for Study 10-201, 200 patients (44%) had any grade hypertension, which includes 52 patients (12%) with Stage 2 hypertension.

**Reviewer Comment (2):** The control of treatment-emergent hypertension in Study 10-201 was not optimal as evidenced by the 44% of patients with hypertension at the last visit.

**Reviewer Comment (3):** The association of treatment-emergent hypertension with ponatinib treatment is notable. The USPI for other FDA-approved TKIs for CML (imatinib, dasatinib, nilotinib, and bosutinib) do not include hypertension as a significant adverse event. However, other kinase inhibitors such as sorafenib, sunitinib, pazopanib, axitinib, and regorafenib are associated with hypertension. The broader spectrum of kinase inhibition observed with ponatinib as compared to other bcr-abl TKIs, may explain why hypertension was only observed with ponatinib. Specifically, inhibition of VEGF-pathway kinases would be consistent with VEGF-inhibitor like AEs observed with ponatinib such as arterial thromboembolic events and gastrointestinal perforation.

**Reviewer Comment (4):** Reversible Posterior Leukoencephalopathy Syndrome (RPLS), also known as Posterior Reversible Encephalopathy Syndrome (PRES), is included in the USPI Warnings and Precautions of the following drugs that inhibit VEGF signaling: pazopanib, axitinib, regorafenib, bevacizumab, and ziv-aflibercept. No cases of RPLS have been reported in patients treated with ponatinib. Given that ponatinib inhibits VEGFR1 and VEGFR2, in addition to the strong association of ponatinib treatment with hypertension (a known risk factor for development for RPLS), a case could be made to include RPLS in the ponatinib label as an anticipated Warning and Precaution. This approach is recognized in the FDA Guidance for Warnings and Precautions (Section II.A.3) wherein an anticipated adverse reaction may be included in the label.

Patients on ponatinib treatment who developed altered new-onset consciousness, visual disturbances, seizures, whether or not associated with hypertension should undergo urgent neuroimaging to evaluate for the presence for RPLS.

#### 7.3.4.7 Congestive heart failure

The incidence of congestive heart failure in Study 10-201 was 6% (any grade), 4% (Grades 3-5), and 4% (serious AE). Preceding or concurrent myocardial ischemia was reported in 41% of patients who experienced CHF as a serious AE. Congestive heart failure or decreased ejection fraction lead to dose modifications in 9 patients, and treatment discontinuation in 3 patients.

Echocardiograms were required assessments for all patients at baseline and at the end of cycle 3. Ninety-seven percent of patients (437/449) had a baseline ejection fraction (EF) assessment, and 80% of patients (357/449) had at least 1 post-baseline echocardiogram follow-up for EF. The baseline EF was  $\geq 50\%$  in 424 patients (94%). Fifteen patients (4% of patients with baseline and follow-up EF data) experienced an EF decline of  $\geq 20\%$  from baseline, and 175 patients experienced a decline of  $<20\%$  from baseline EF (49% of patients with baseline and follow-up EF data). Twenty-three patients with a baseline EF of  $\geq 50\%$  had a post-baseline EF of  $<50\%$ .

The median time-to-onset for clinical cardiac failure (excludes echocardiogram findings) was 153 days. The median time-to-onset for all cardiac failure (includes echocardiogram findings) was 85 days.

**Reviewer Comment:** Congestive heart failure is not unexpected with TKI treatment in patients with CML or Ph+ALL. The Warnings and Precautions sections of the USPI for imatinib and dasatinib include cardiac failure.

#### 7.3.4.8 Cardiac Conduction Defects including Prolonged QTc

Symptomatic bradyarrhythmias that lead to a requirement for pacemaker implantation occurred in 3 patients. The underlying cardiac rhythms (1 case each) were complete heart block, sick sinus syndrome, and atrial fibrillation with bradycardial conduction and pauses. In the expanded access program, a 70 year old female patient (GB000850) collapsed at home and was documented to have complete heart block.

QTc prolongation was reported as an AE in 6 patients (1.3%) in Study 10-201. There were no cases of Torsade de Pointes in Study 10-201.

Analysis of the VS dataset identified 12 patients with pulse rate  $\leq 50$  bpm and decline of  $\geq 10$  bpm from the baseline pulse rate. In 9 of these 12 patients, concomitant medications with negative chronotropic effects were identified (e.g., betablockers, diltiazem, verapamil, clonidine), which were initiated due to occurrence of hypertension.

Refer to Section 7.4.4 for analysis of ECG data in Study 10-201.

#### 7.3.4.9 Atrial Fibrillation and Supraventricular Tachyarrhythmias

Supraventricular tachyarrhythmias occurred in 22 patients (5%). Atrial fibrillation was the most common supraventricular tachyarrhythmia and occurred in 17 patients. The other supraventricular tachyarrhythmias were atrial flutter (4 patients), supraventricular tachycardia (4 patients), and atrial tachycardia (1 patient). Eleven patients experienced a serious event which lead to hospitalization. All of the cases of supraventricular tachyarrhythmias occurred in patients older than 60 years of age. Most of the patients also had underlying cardiovascular risk factors. There was no association between the occurrence of atrial fibrillation and the occurrence of stroke or TIA in Study 10-201.

**Reviewer Comment:** The occurrence of atrial fibrillation and supraventricular tachyarrhythmias may be a manifestation of cardiac toxicity or irritability possibly from a primary drug effect or secondarily from concomitant issues such as ischemia and hypertension.

Refer to Section 7.4.4 for analysis of ECG data in Study 10-201.

#### 7.3.4.10 Venous Thromboembolic Events

Venous thromboembolic events occurred in 14 patients (3%). The venous thromboembolic events consisted of deep venous thrombosis (8 patients), pulmonary embolism (4 patients), portal vein thrombosis (1 patient), and retinal vein thrombosis (1 patient). Eight patients experienced VTE as a serious event.

#### 7.3.4.11 Gastrointestinal perforation and wound healing complications

Gastrointestinal perforation and wound healing complications are known safety issues with kinase inhibitors that inhibit VEGF receptors. Patient 785002 in Study 10-201 developed an enterocutaneous fistula on D<sup>(b)(6)</sup> of ponatinib treatment; patient had undergone prior laparoscopic cholecystectomy on D<sup>(b)(6)</sup>. Patient underwent resection of a jejunal loop with an unremarkable post-operative course. Recurrent peripheral ischemia associated with extremity necrosis occurred in 2 patients in Study 10-201.

**Reviewer Comment:** Gastrointestinal perforation and temporary interruption for surgical procedures are included in the Warnings and Precautions section of the USPI for the following kinase inhibitors that inhibit VEGFR1 or VEGFR2: sorafenib, pazopanib, axitinib, and regorafenib. The USPI imatinib includes gastrointestinal perforation in the Warnings and Precautions section.

#### 7.3.4.12 Fluid Retention

Fluid retention (not including congestive heart failure) of any grade was reported in 18% of the patients. There were 10 patients who experienced a fluid retention SAE (pericardial effusion, pleural effusion, or ascites). The fluid retention incidence (with inclusion of AE terms related to congestive heart failure or pulmonary hypertension) was 22%.

#### 7.3.4.14 Tumor Lysis Syndrome and Hyperuricemia

Three patients experienced tumor lysis syndrome (Grade 4 in 2 patients, Grade 1 in 1 patient). Patient 003-001 was a 61/F with AP-CML who experienced G4 TLS on day 4 of treatment, and presented with fatigue, altered mental status, and acute renal failure. Initial labs were notable for potassium of 6 mmol/L, uric acid >27 mg/dL, creatinine 4.8 mg/dL. Patient received hydration, allopurinol, 3 doses of rasburicase and recovered from the TLS event. The second case of G4 TLS occurred in a patient who discontinued ponatinib due to disease progression on 12/29/10, and subsequently experienced G4 TLS after initiation of hydroxyurea and nilotinib on 12/31/10.

Twenty-six patients (6%) experienced any grade of hyperuricemia. Seven patients experienced G3-4 hyperuricemia. Eleven patients received rasburicase during ponatinib treatment. The indications for rasburicase were tumor lysis treatment or prevention, or treatment of hyperuricemia.

#### 7.3.4.13 Dermatologic Toxicity

The most common dermatologic AEs were rash and dry skin, with incidences of 49% and 33%, respectively. Grade 3 rash was reported in 6% of patients. There were no events of grade 4 rash. There were no cases of hand-foot syndrome or palmoplantar erythrodysesthesia.

#### 7.3.4.14 Other Toxicities

Mucositis. Oral ulcers and mucositis are adverse events associated with VEGFR-kinase inhibitors (sunitinib, axitinib, pazopanib). In Study 10-201, 55 patients (13%) developed adverse events related to oral mucositis, oral pain, or oral ulceration.

Proteinuria. Monitoring for proteinuria was not done for Study 10-201. In Study 07-101, 27 of the 81 patients (33%) experienced treatment-emergent proteinuria<sup>3</sup>. Ten patients (12%) had a post-baseline level of 100 mg/dL or greater. Two patients had treatment-emergent proteinuria of  $\geq 300$ mg/dL. Quantitative urine protein analysis was not performed in Study 07-101.

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<sup>3</sup> Trace protein on dipstick testing was not included in the calculations.

Thyroid dysfunction. Hypothyroidism is an adverse event associated with VEGFR-kinase inhibitors (sunitinib, axitinib, pazopanib). Eight patients (2%) in Study 10-201 experienced treatment-emergent hypothyroidism. However, TSH was not part of routine monitoring in Study 10-201.

In Study 07-101, TSH was monitored on day 1 of each cycle, day 15 of Cycles 1 and 2, and at the end-of-treatment visit. Twenty-one patients (24%) developed treatment-emergent elevation of TSH (defined as greater than ULN and greater than baseline TSH) during follow-up.

Neuropathy. Forty-six patients (10%) experienced treatment-emergent peripheral neuropathy. Majority of the cases were G1-2 neuropathy. Five patients experienced Grade 3 peripheral neuropathy. There was no association between diabetes and the development of treatment-emergent peripheral neuropathy (10.7% in patients with diabetes, 10.2% in non-diabetic patients).

Cranial nerve neuropathy occurred in 4 patients in Study 10-201. Two cases were SAEs: CN4 palsy (SUBJID 127-008) and combined CN3 CN7 palsy (SUBJID 957-01). The other 2 cases were CN6 palsy and facial neuralgia.

### 7.3.5 Submission Specific Primary Safety Concerns

Refer to Section 7.3.4.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

**Table 45 Treatment-Emergent Adverse Events  $\geq$  10% in any Disease Cohort in Study 10-201**

System Organ Class Preferred Term	CP-CML N=270		AP-CML N=85		BP-CML N=62		Ph+ ALL N=32	
	Any Grade (%)	G3-4 (%)	Any Grade (%)	G3-4 (%)	Any Grade (%)	G3-4 (%)	Any Grade (%)	G3-4 (%)
<b>Cardiac or Vascular</b>								
Arterial Occlusive or Thromboembolic Event	11	6	8	5	6	5	3	0
Hypertension (a) (AE) (VS)	19 74	6 40	13 73	7 40	18 66	5 26	25 53	9 31
Congestive heart failure (b)	5	2	6	2	13	8	6	3
<b>Gastrointestinal</b>								
Abdominal pain (c)	40	9	33	8	32	6	34	6
Constipation	36	2	22	2	24	0	47	3
Nausea	22	1	24	0	31	2	22	0
Diarrhea	16	1	24	0	18	3	9	3
Vomiting	13	2	24	0	23	2	19	0
Oral mucositis (d)	10	<1	15	1	26	0	9	3
GI hemorrhage (e)	2	0	8	1	11	3	9	6
<b>Blood and lymphatic system</b>								
Febrile neutropenia	1	<1	4	4	11	10	25	25
<b>Infections and infestations</b>								
Upper respiratory tract infection	11	1	5	0	11	2	0	0
Urinary tract infection	7	<1	12	1	0	0	9	0
Nasopharyngitis	8	0	11	0	3	0	3	0
Pneumonia	4	1	11	8	15	13	13	6
Cellulitis	1	1	4	2	11	3	0	0
Sepsis	1	1	2	1	5	2	19	13
<b>Nervous system</b>								
Headache	37	3	26	0	31	3	25	0
Peripheral neuropathy (f)	12	2	7	0	8	0	6	0
Dizziness	10	0	5	0	5	0	3	0
<b>Respiratory, thoracic, and mediastinal</b>								
Cough	12	0	15	0	18	0	6	0
Dyspnea	9	1	13	1	21	7	6	0

System Organ Class Preferred Term	CP-CML N=270		AP-CML N=85		BP-CML N=62		Ph+ ALL N=32	
	Any Grade (%)	G3-4 (%)	Any Grade (%)	G3-4 (%)	Any Grade (%)	G3-4 (%)	Any Grade (%)	G3-4 (%)
Pleural effusion	3	<1	9	1	13	0	19	3
<b>Skin and subcutaneous tissue</b>								
Rash and related conditions	53	5	47	9	39	5	34	6
Dry skin	37	2	27	1	24	2	25	0
<b>General</b>								
Fatigue	38	3	34	6	34	5	31	3
Pyrexia	21	1	29	5	32	3	25	0
Peripheral edema	10	<1	14	0	11	0	22	0
Pain	9	<1	6	0	16	3	6	0
Chills	7	0	9	0	13	2	9	0
<b>Musculoskeletal</b>								
Arthralgia	26	2	31	1	18	0	13	0
Myalgia	21	1	20	0	13	0	6	0
Pain in extremity	16	2	14	0	13	0	9	0
Back pain	14	1	9	1	16	2	13	0
Muscle spasms	12	0	4	0	5	0	13	0
Bone pain	12	<1	12	1	10	3	16	3
<b>Investigations</b>								
Weight decreased	6	<1	6	0	5	0	13	0
<b>Metabolism and nutrition</b>								
Decreased appetite	8	<1	11	1	8	0	31	0

(a) includes BP increased, SBP increased, hypertension, hypertensive crisis

(b) includes cardiac failure, cardiac failure congestive, cardiogenic shock, cardiopulmonary failure, ejection fraction decreased, pulmonary edema, right ventricular failure

(c) includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort

(d) includes aphthous stomatitis, lip blister, mouth ulceration, oral mucosal eruption, oral pain, oropharyngeal blistering, oropharyngeal discomfort, oropharyngeal pain, pharyngeal erythema, pharyngeal ulceration, stomatitis, tongue eruption, tongue ulceration

(e) includes gastric hemorrhage, gastric ulcer hemorrhage, hemorrhagic gastritis, gastrointestinal hemorrhage, hematemesis, hematochezia, hemorrhoidal hemorrhage, intra-abdominal hemorrhage, melena, rectal hemorrhage, and upper gastrointestinal hemorrhage

(f) includes burning sensation, hyperesthesia, hypoesthesia, neuralgia, peripheral neuropathy, paresthesia, polyneuropathy

### 7.4.2 Laboratory Findings

**Table 46 Treatment-Emergent Laboratory Abnormalities  $\geq$  10% in any Disease Cohort in Study 10-201**

	CP-CML N=270		AP-CML N=85		BP-CML N=62		Ph+ ALL N=32	
	Any Grade (%)	G3-4 (%)	Any Grade (%)	G3-4 (%)	Any Grade (%)	G3-4 (%)	Any Grade (%)	G3-4 (%)
<b>Hematology</b>								
Thrombocytopenia (platelets decreased)	61	34	76	47	50	44	50	47
Neutropenia (ANC decreased)	46	23	75	47	60	48	69	59
Anemia (Hgb decreased)	40	9	52	24	61	52	75	41
Lymphopenia	31	9	56	24	60	32	59	19
Leukopenia (WBC decreased)	53	12	81	33	69	48	75	63
<b>Pancreatic enzymes</b>								
Lipase increased	23	11	25	9	11	7	9	3
Amylase increased	2	0	2	0	5	3	0	0
<b>Liver function tests</b>								
ALT increased	47	6	58	8	52	13	28	9
AST increased	39	3	31	2	42	5	22	0
Alkaline phosphatase increased	32	1	31	1	47	5	38	3
Bilirubin increased	12	<1	27	4	19	0	13	3
Albumin decreased	23	<1	25	0	27	0	25	0
<b>Chemistry</b>								
Phosphorus decreased	60	6	51	8	32	11	34	3
Calcium decreased	46	<1	47	1	42	2	47	0
Glucose increased	54	5	56	6	44	0	38	0
Glucose decreased	24	0	27	0	15	0	9	0
Potassium decreased	8	1	21	4	18	3	9	0
Sodium decreased	26	4	31	6	27	2	16	3
Potassium increased	13	2	11	1	15	5	13	0
Sodium increased	11	<1	8	0	5	0	6	0
Bicarbonate decreased	10	<1	7	0	13	0	6	0

### 7.4.3 Vital Signs

Refer to Section 7.3.4 regarding evaluation for hypertension.

#### 7.4.4 Electrocardiograms (ECGs)

##### Study 07-101

Refer to IRT and Clinical Pharmacology Review. The Applicant submitted a clinical cardiac report for a subset of 39 patients enrolled in Study 07-101. A summary of the analysis is shown in Table 47.

**Table 47 Study 07-101 Mean Change from Baseline and New Outliers by Dose Group**

	Ponatinib 30 mg	Ponatinib 45 mg	Ponatinib 60 mg
Sample Size	6	21	12
Heart Rate in bpm (mean change from baseline)	3.5	-3.3	1.0
Heart Rate Bradycardic Outliers N (%)	0 (0%)	0 (0%)	0 (0%)
Heart Rate Tachycardic Outliers N (%)	0 (0%)	1 (5%)	1 (8%)
PR in ms (mean change from baseline)	-0.4	-3.6	-0.7
PR Outliers N (%)	0 (0%)	0 (0%)	0 (0%)
QRS in ms (mean change from baseline)	-0.8	1.3	3.6
QRS Outliers N (%)	0 (0%)	0 (0%)	0 (0%)
QT in ms (mean change from baseline)	-13.4	3.3	-4.6
QT new >500 ms N (%)	0 (0%)	1 (5%)	0 (0%)
QTcF in ms (mean change from baseline)	-10.9	-3.6	-5.0
QTcF new >500 ms N (%)	0 (0%)	1 (5%)	0 (0%)
QTcF new >480 ms N (%)	0 (0%)	1 (5%)	0 (0%)
QTcF 30-60 ms N (%)	0 (0%)	3 (14%)	0 (0%)
QTcF >60 ms N (%)	0 (0%)	0 (0%)	1 (8%)
QTcB in ms (mean change from baseline)	-9.2	-7.4	-4.9
QTcB new >500 ms N (%)	0 (0%)	0 (0%)	0 (0%)
QTcB new >480 ms N (%)	0 (0%)	1 (5%)	1 (8%)
QTcB 30-60 ms N (%)	1 (17%)	2 (10%)	0 (0%)
QTcB >60 ms N (%)	0 (0%)	0 (0%)	1 (8%)
New abnormal U waves N (%)	0 (0%)	0 (0%)	0 (0%)
New ST segment depression or elevation N (%)	0 (0%)	0 (0%)	0 (0%)
New T wave inversion N (%)	0 (0%)	1 (5%)	1 (8%)
New Second or Third Degree Heart Block N (%)	0 (0%)	0 (0%)	0 (0%)
New RBBB or LBBB N (%)	0 (0%)	0 (0%)	0 (0%)
New Atrial Flutter N (%)	0 (0%)	0 (0%)	0 (0%)
New Atrial Fibrillation N (%)	1 (17%)	0 (0%)	1 (8%)
New MI N (%)	0 (0%)	0 (0%)	0 (0%)

bpm=beats per minute; ms=milliseconds; QTcF= Fridericia correction; QTcB: Bazett correction; LBBB= left bundle branch block; RBBB=right bundle branch block; AF= atrial fibrillation/flutter; MI=myocardial infarction pattern; “new” means not present at baseline, i.e. at any evaluation pre dose, and only seen post baseline.

Source: Clinical Cardiac Report for Study 07-101, page 20 (Module 5.3.5.2.3)

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### Study 10-201

Electrocardiograms (ECGs) were required at screening, Cycle 2 Day 1, Cycle 3 Day 28, and at the end of treatment. All patients had a screening ECG. The number of patients who had follow-up ECGs that were evaluable for QTc interval at the prespecified milestones include: Cycle 2 Day 1 (388 patients, 86%), Cycle 3 Day 28 (341 patients, 76%), and end-of-treatment (106 patients, 24%).

Analysis of QTcF data from Study 10-201 (EG.xpt dataset) included 426 patients with baseline and at least 1 follow-up ECG evaluable for QTcF. Twenty-one patients (5%) had treatment emergent prolongation of QTcF; 18 with G1 QTcF prolongation (450-480ms) and 3 patients with G2 QTcF prolongation (481-500ms). Forty-two patients (10%) had at least 30 ms QTcF prolongation compared to baseline: 8 patients had >60 ms QTcF prolongation compared to baseline, 34 patients had 30-60 ms QTcF prolongation compared to baseline. Overall, 50 patients (12%) had treatment-emergent QTcF prolongation or  $\geq 30$  ms prolongation of QTcF as compared to baseline.

When combined with the AE data, 25 patients (5.6%) in Study 10-201 experienced treatment-emergent QTc prolongation. All cases were G1-2 except for 1 patient (SUBJID 939-003) with G3 prolongation.

Analysis of ECG rhythm data (EG.xpt dataset) was notable for additional findings on conduction delays and supraventricular tachyarrhythmias.

Seventeen patients (4%) had conduction delays on follow-up ECGs that were not present on the baseline ECG. The conduction delays include RBBB, first-degree AV block, non-specific intraventricular conduction delay, LBBB, and fascicular blocks. When combined with the AE data, 19 patients (4%) experienced conduction delays.

Thirteen patients (3%) had supraventricular tachyarrhythmia documented on follow-up ECGs that were not present on the baseline ECG. The supraventricular rhythms include atrial fibrillation (6), SVT (5), atrial tachycardia (1), and atrial flutter (1). When combined with the AE dataset, 33 patients (7%) experienced supraventricular tachyarrhythmias. The supraventricular rhythms include atrial fibrillation (22), SVT (9), atrial flutter (5), and atrial tachycardia (2).

**Reviewer Comment:** The frequency of QTc prolongation and rhythm abnormalities (including conduction delays and supraventricular tachyarrhythmias) was likely underestimated in Study 10-201 due to the paucity of ECG monitoring. Also, ECG monitoring in Study 10-201 occurred predominantly at earlier timepoints. Only 22% of the patients had ECGs performed after day 90.

#### 7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

#### 7.4.6 Immunogenicity

The application did not contain information regarding evaluation for immunogenicity.

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

Refer to the clinical pharmacology and pharmacometrics review for exposure-response analysis related to dose intensity for Study 10-201. Because pharmacokinetic samples were not obtained in Study 10-201, exposure-response analysis was limited to dose intensity information.

#### 7.5.2 Time Dependency for Adverse Events

Time-to-event analyses were integrated in Section 7.3.4.

#### 7.5.3 Drug-Demographic Interactions

Arterial occlusive or thromboembolic event and demographic interaction was integrated in Section 7.3.4.1.

#### 7.5.4 Drug-Disease Interactions

Arterial occlusive or thromboembolic event and disease interaction was integrated in Section 7.3.4.1.

#### 7.5.5 Drug-Drug Interactions

Refer to Clinical Pharmacology Review.

Nonclinical data suggest that cytochrome P450 3A4 (CYP3A4) is involved in the human metabolism of ponatinib. In the clinical studies in patients, concomitant use of CYP3A4 inhibitors was discouraged, but not prohibited.

The Applicant conducted a study to determine whether concurrent administration of the CYP3A4 inhibitor ketoconazole would inhibit the metabolism of a single dose of ponatinib in healthy subjects (Clinical Study Report AP24534-11-103).

- Subjects were randomized to a treatment sequence on Day -1. In the ponatinib-alone period, subjects received a single 15-mg dose of ponatinib on Day 1, with pharmacokinetic sampling at various intervals through 96 hours post-dose. In the ponatinib-plus-ketoconazole period, subjects received 400 mg ketoconazole in the evening of Day -1, and then daily through Day 4, with the single dose of 15 mg ponatinib on Day 1. Pharmacokinetic sampling was done as for the ponatinib-alone period.
- Concurrent administration of multiple doses of ketoconazole with single-dose ponatinib (15 mg) resulted in a 78% and 47% increase in plasma ponatinib  $AUC_{0-\infty}$  and  $C_{max}$ , respectively, without affecting time to achieve maximum plasma concentrations. Multiple-dose ketoconazole coadministration also resulted in a 70% decrease in plasma exposure to AP24567 (a metabolite of ponatinib).

To further characterize the importance of CYP3A4/5 on the overall pharmacokinetic profile of ponatinib and the potential for gastric pH mediated drug-drug interactions with ponatinib, the Applicant is in the process for development of studies evaluating the concomitant administration of rifampicin and lansoprazole with ponatinib.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

Refer to Pharmacology-Toxicology review regarding planned nonclinical studies for assessment of carcinogenicity of ponatinib.

Human carcinogenicity cannot be adequately evaluated in this application due to the following limitations: no control arm, small safety population (N=530), short duration of follow-up, and confounding effects of prior treatments in the patient population.

### 7.6.2 Human Reproduction and Pregnancy Data

As of 01 June 2012, no pregnancies have been reported in women or in the female partners of men who have been exposed to ponatinib.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

Ponatinib has not been studied in patients younger than 18 years of age.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Four patients (2 in Study 07-101 and 2 in Study 10-201) experienced ponatinib overdose as defined by the protocol:

- Patient 075-0006 (CP-CML; phase 1 study) in the 60 mg cohort had a grade 1 SAE of accidental overdose. The patient inadvertently self-administered thirty-three, 5 mg capsules (165 mg) of ponatinib on cycle (b) (6). The prescribed dose was twelve 5-mg capsules. A complete blood count and ECG obtained approximately 24 hours after the overdose were normal. Patient experienced fatigue and non-cardiac chest pain on C (b) (6). Ponatinib was held for 5 days and restarted without incident.
- Patient 005-0032 (AML; phase 1 study) in 45 mg cohort of the phase 1 study had a grade 2 SAE of accidental overdose. On (b) (6), while hospitalized for the SAEs of pneumonia and sepsis, the patient was accidentally administered the entire contents of the bottle of study medication via nasogastric tube. The investigator estimated that the patient received 540 mg of ponatinib. After discovery of the error (the next day), the patient was monitored by serial ECG. Two hours after the overdose, the ECG revealed normal sinus rhythm with a prolonged, uncorrected QT interval of 0.52 seconds. Subsequent ECGs on the following 2 days revealed normal sinus rhythm with uncorrected QT intervals of 0.48 seconds and 0.40 seconds, respectively. On (b) (6), amylase and lipase levels were reportedly normal. Patient died (b) (6) days after the overdose from pneumonia and sepsis.
- Patient 945-002 (phase 2 study) was a 70 year-old female with CP-CML who misunderstood written directions and inadvertently self-administered ponatinib, 90 mg, once daily the first (b) (6) days on study drug. She was hospitalized with pneumonia and systemic inflammatory response (SIRS) and study drug was interrupted. The patient developed atrial fibrillation the day after hospital admission and asymptomatic, moderate pericardial effusion (b) (6) days post-admission which was suspected by the investigator to be due to septicemia. The events resolved, and ponatinib was restarted at 45 mg, once daily.
- Patient 958-002 (phase 2 study) was a 37 year-old male with Ph+ ALL who had been treated previously with stem cell transplant. Relevant medical history includes diabetes mellitus and disseminated intravascular coagulation, which was ongoing at the time of enrollment. Ponatinib 45 mg once daily was initiated on (b) (6). The patient experienced fluid retention on (b) (6) and was treated with furosemide. The investigator increased the ponatinib dose to 60 mg, (considered an “overdose” per protocol and a protocol violation, as doses greater than 45 mg are not allowed) once daily on (b) (6) for lack of efficacy. On (b) (6) the patient was hospitalized with pleural and pericardial effusions. He was treated with diuretics and lost 3 kg during hospitalization with improvement in respiratory level and almost complete disappearance of edema. The event of fluid retention resolved on (b) (6). The investigator assessed the fluid retention as probably related to ponatinib. Ponatinib 60 mg once daily was continued until (b) (6) when it was withdrawn for progressive disease.

Ponatinib does not appear to have an abuse potential based on its chemical and pharmacologic properties and mechanism of action.

### **7.7 Additional Submissions / Safety Issues**

The Applicant submitted the 120-day safety report on October 2012. The updated data cut-off date was July 23, 2012. Notable safety signals identified in the 120-day safety update report include increased incidence of arterial occlusive and thromboembolic events (discussed in Section 7.3.4.1) and two cases of fatal acute hepatic failure (discussed in Section 7.3.4.2).

## **8 Postmarket Experience**

Ponatinib is a new molecular entity in the United States. No U.S. postmarketing information is available. Ponatinib is not marketed outside of the U.S.

## 9 Appendices

### 9.1 Literature Review/References

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## 9.2 Labeling Recommendations

Labeling recommendations were integrated in the body of the review.

## 9.3 Advisory Committee Meeting

This application was not taken to ODAC (Oncologic Drugs Advisory Committee).

Consultation was planned with two Special Government Employee clinical consultants and one patient representative. At the time of this review finalization, one clinical consultant and one patient representative have been cleared by the Advisors and Consultants staff. The results of the consults will be included in the CDTL review or as an addendum to this review or the CDTL review.

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/s/  
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ROMEO A DE CLARO  
11/19/2012

VIRGINIA E KWITKOWSKI  
11/19/2012

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number: 203469    Applicant: ARIAD  
Pharmaceuticals, Inc.**

**Stamp Date: Part 1 (30 July 2012),  
Part 2 (27 September 2012)**

**Drug Name: Ponatinib            NDA/BLA Type: 505(b)(1)**

On initial overview of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
<b>DOSE</b>					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? <b>Study Number:</b> AP24534-07-101 <b>Study Title:</b> A Phase 1 Dose Escalation Trial to Determine the Safety, Tolerability and Maximum Tolerated Dose of Oral AP24534 in Patients with Refractory or Advanced Chronic Myelogenous Leukemia and other Hematologic Malignancies <b>Sample Size:</b> 81 <b>Arms:</b> 10 dosing cohorts (ponatinib dose range 2 mg to 60 mg per day) <b>Location in submission:</b> Module 5.3.5.2	X			

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
<b>EFFICACY</b>					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Yes  <b>Pivotal Study #1</b> <b>Study Number:</b> AP24534-10-201 <b>Study Title:</b> A Pivotal Phase 2 Trial of Ponatinib (AP24534) in Patients with <span style="background-color: #cccccc; padding: 0 2px;">(b) (4)</span> Chronic Myeloid Leukemia and Ph+ Acute Lymphoblastic Leukemia <b>Sample Size:</b> 449 <b>Arms:</b> single-arm trial (6 cohorts) <b>Location in submission:</b> Module 5.3.5.2  Pivotal Study #2 (None submitted)	X			Submission of a single pivotal study and confirmatory evidence is an acceptable basis for an application as per FDAMA.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			186 of 449 (41%) in Study 10-201 were U.S. patients.
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			Minor revisions in safety dataset format requested.
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	X			Minor revisions in safety dataset format requested.

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Applicant submitted a pediatric waiver. Orphan designation was granted on 20 Nov 2009.
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	See #17.
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			Minor revisions in safety dataset format requested.
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			Minor revisions in safety dataset format requested.
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all	X			

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## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?				

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Not applicable.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Review issues will be sent to the Applicant through separate cover.

R. Angelo de Claro, M.D.	28 September 2012
Reviewing Medical Officer	Date

Virginia Kwitkowski, MS, RN, ACNP-BC	28 September 2012
Clinical Team Leader	Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ROMEO A DE CLARO  
09/28/2012

VIRGINIA E KWITKOWSKI  
09/28/2012