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

NCT Number: NCT02467270

SAP Approve Date: 17 December 2019

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# STATISTICAL ANALYSIS PLAN

## FOR

## AP24534-14-203

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

**PROTOCOL NUMBER:** AP24534-14-203

**IND NUMBER:** 78,375

**SPONSOR:**
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**ORIGINAL ISSUE DATE:** Version 2.2 17 December 2019

**REVISION/AMENDMENT HISTORY:**

| Amendment Version | Version Number | Date |
|---|---|---|
| Protocol Amd 4.0 | 1.0 | 06 June 2017 |
| Protocol Amd 5.0 | 2.1 | 06 August 2019 |

## TABLE OF CONTENTS

## LIST OF ABBREVIATIONS

| Abbreviation | Term |
|---|---|
| AE | adverse event |
| AOE | arterial occlusive event |
| AP | accelerated phase |
| AUC | area under the curve |
| ARIAD | ARIAD Pharmaceuticals, Inc. |
| BCR-ABL1 | Breakpoint Cluster Region-Abelson |
| BCR-ABL$^{IS}$ | BCR-ABL1 transcript level as measured by the International Scale |
| BM | bone marrow |
| BMI | body mass index |
| BP | blast phase |
| CBC | complete blood count |
| CCyR | complete cytogenetic response |
| CHR | complete hematologic response |
| CI | confidence interval |
| CM | concomitant medication |
| CML | chronic myelogenous leukemia/chronic myeloid leukemia |
| $C_{max}$ | maximum plasma concentration |
| CP | chronic phase |
| CTCAE | Common Terminology Criteria for Adverse Events |
| EAIR | exposure-adjusted incidence rate |
| ECG | Electrocardiogram |
| ECHO | Echocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| CCI | [redacted] |
| ITT | Intent-to-Treat |
| LEUS | leukemia subscale |
| MCyR | major cytogenetic response |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MR1 | molecular response with 1-log reduction |
| MMR | molecular response with 3-log reduction |
| MR4 | molecular response with 4-log reduction |
| MR4.5 | molecular response with 4.5-log reduction |
| NCI | National Cancer Institute (of the United States) |
| OS | overall survival |
| PCR | polymerase chain reaction |
| PCyR | partial cytogenetic response |
| PFS | progression-free survival |

| Abbreviation | Term |
|---|---|
| Ph+ | Philadelphia chromosome positive |
| PK | pharmacokinetic(s) |
| PP | per-protocol |
| CCI | [redacted] |
| QD | once daily |
| QTcF | QT interval corrected (Fridericia) |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SMQ | Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query |
| SOC | system organ class |
| CCI | [redacted] |
| TEAE | treatment-emergent adverse event |
| TKI | tyrosine kinase inhibitor |
| TOI | trial outcome index |
| ULN | upper limit of normal |
| VAS | visual analog scale |
| VTE | venous thromboembolic event |
| WHO | World Health Organization |

# 1 INTRODUCTION

This Statistical Analysis Plan describes the design characteristics and statistical analysis methods for the study. It specifies the statistical approaches and data handling conventions for key analyses that include the primary analysis for the primary endpoint and the analyses for secondary endpoints, based on the Protocol Version 6.0.

# 2 STUDY OBJECTIVES AND ENDPOINTS

## 2.1 Study Objectives

### 2.1.1 Primary Objective

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

### 2.1.2 Secondary Objectives

- To characterize the rate of major molecular response (MMR) at 12 months and 24 months and rate of major cytogenetic response (MCyR) at 12 months
- To evaluate duration of MMR
- To characterize the rates of AOEs, VTEs, AEs, and SAEs.
- To evaluate safety differences among the 3 starting dose cohorts, particularly for AOEs and VTEs.
- To characterize the exposure-response and exposure-toxicity relationships between PK parameters and selected safety and efficacy measures.

### 2.1.3 Other Secondary Objectives

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

### 2.1.4 Exploratory Objectives

CCI [redacted]

## 2.2 Study Endpoints

### 2.2.1 Primary Endpoint

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

### 2.2.2 Secondary Endpoints

- Efficacy
    a. Molecular response rates: MMR at 12 and 24 months
    b. Cytogenetic response rates: MCyR at 12 months
    c. Duration of MMR
- Safety
    a. Rate of AOEs and VTEs in each dose cohort
    b. Rate of AEs in each dose cohort
    c. Rate of SAEs in each dose cohort
- Exposure-response and exposure-toxicity relationships of AUC and $C_{max}$ at steady-state on efficacy outcomes (including MCyR, ≤ 1% BCR-ABL1$^{IS}$, and MMR) and on safety outcomes (including AOEs and VTEs)

### 2.2.3 Other Secondary Endpoints

- Cytogenetic response rates: CCyR at 12 months
- Molecular response rates:
    a. MR4, and MR4.5 at and by 3-month intervals
    b. MR1 (≤ 10% BCR-ABL1$^{IS}$) at 3 months
- Hematologic response rates: CHR at 3 months
- Tolerability:
    a. Rate of discontinuation due to AEs in each dose cohort
    b. Dose reductions due to AEs in each dose cohort
    c. Dose interruptions in each dose cohort
- Duration of response:
    a. Rates of ≤ 1% BCR-ABL1$^{IS}$ by 12 months and at and by 6, 18, and 24 months
    b. MMR at and by 6 and 18 months; and by 12 and 24 months
- Duration of response in responders
- Time to response

- Rate of progression to AP- or BP-CML
- PFS
- OS

### 2.2.4 Exploratory Endpoints

CCI [redacted]

# 3 STUDY DESIGN

## 3.1 Study Design

This is a multi-center, randomized, open-label, phase 2 trial to characterize the efficacy of ponatinib over a range of 3 starting doses. Eligible patients must have CP-CML, have received at least 2 prior TKI therapies with demonstrated resistance to treatment or have the T315I mutation, and > 1% BCR-ABL1$^{IS}$ (. The trial will also assess the short- and long-term safety of the 3 starting doses investigated.

Patients will be randomized to receive once-daily oral administration of 1 of 3 starting doses of ponatinib: 45 mg (Cohort A), 30 mg (Cohort B), or 15 mg (Cohort C). Patients starting at 45 mg or 30 mg will have their daily dose reduced to 15 mg upon achievement of ≤ 1% BCR-ABL1$^{IS}$, as described in the protocol Section 14.1.3. In the event of loss of ≤ 1% BCR-ABL1$^{IS}$ (as defined in Section 16.5.1.1of the protocol) after dose reduction for response, and in the absence of AEs necessitating continued dose reduction, escalation back to the starting dose will be allowed, upon review and agreement with the medical monitor.

Total study duration is expected to be approximately 60 months. This includes an enrollment period of approximately 36 months and a duration of treatment with study drug of 24 months, unless the patient is discontinued early. Patients will be followed for 30 days after last dose of study drug.

## 3.2 Blinding

This study is an open-label study; patients, investigators, and the sponsor will know the identity of each patient's study treatment.

## 3.3 Randomization

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

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

The randomization will be stratified based on the patient's baseline age (≥ 60 vs < 60 years) and history of hypertension, diabetes, and/or hyperlipidemia (yes/no). Randomization procedures should be performed following complete eligibility assessments and prior to the initiation of assigned treatment.

### 3.4 Study Treatment

Patients will be randomized to receive once-daily oral administration of 1 of 3 starting doses of ponatinib: 45 mg QD (Cohort A), 30 mg QD (Cohort B), or 15 mg QD (Cohort C). A cycle of therapy will comprise 28 days of treatment, regardless of dose.

#### 3.4.1 Mandatory Dose Reduction

Patients will undergo assessments for achievement of ≤ 1% BCR-ABL1$^{IS}$ and for consideration of mandatory dose reduction at 3, 6, 9, and 12 months, and those in the 45mg QD and 30mg QD cohorts will have their doses reduced to 15 mg QD upon attainment of ≤ 1% BCR-ABL1$^{IS}$. No dose reduction for response will be implemented for patients in the 15mg QD cohort. The schedule for dose reduction is described in the protocol Section 14.1.3.

#### 3.4.2 Escalation for Loss of Response after Dose Reduction for Achievement of ≤ 1% BCR-ABL1$^{IS}$

Patients who achieve ≤ 1% BCR-ABL1$^{IS}$ at any time point, undergo dose reduction, and then lose ≤ 1% BCR-ABL1$^{IS}$, are candidates for dose re-escalation to their starting dose in the absence of AEs requiring dose modification. The dose re-escalation schema is described in the protocol Section 14.1.4.

### 3.5 Determination of Sample Size

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

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

## 4 STATISTICAL ANALYSES AND METHODS

### 4.1 General Considerations

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

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

Categorical data will be summarized by the number and percentage of patients in each category. Continuous variables will be summarized by descriptive statistics, including mean, standard deviation, median, and range. Two-sided confidence interval will be provided where appropriate.

Statistical inference will be made for each of the 3 cohorts separately—each with the primary endpoint of ≤ 1% BCR-ABL1$^{IS}$ tested at 2-sided 0.05/3=0.0167 significance level, using the Bonferroni method for multiplicity adjustment. The primary analysis of the primary endpoint of ≤ 1% BCR-ABL1$^{IS}$ will be performed using a 2-sided exact 98.3% CI for ≤ 1% BCR-ABL1$^{IS}$ rate based on the ITT population followed through the Main Treatment Period. Any other comparisons will be descriptive. An interim analysis (IA) is planned for this study after all patients have been enrolled in the study. The IA data summary will be descriptive in nature. The primary analysis is planned to be performed when all patients have at least 12 months of treatment. Additional analyses may be performed at later time points to develop additional CSRs as per sponsor's discretion. In addition, the data will be summarized and reported at least annually.

Baseline value is defined as the last valid value on or before the first dose date of study treatment, unless otherwise specified. Missing/partial dates for initial diagnosis date, prior cancer therapy, AE, and CM will be imputed using a conservative approach. The imputation methods are available upon request.

### 4.2 Analysis Populations

There will be 4 main analysis populations for this study.

**ITT Population:** The ITT population will include all patients who are randomized and for whom BCR-ABL$^{IS}$ can be measured (i.e. patients who have the b2a2/b3a2 transcript type), regardless of whether they take the assigned study drug. The primary analyses of molecular efficacy will be based on this population. Randomized patients with the b2a2/b3a2 transcript type without response assessments will be considered as non-responders in the primary efficacy analysis.

**ITT Cytogenetic population**: The ITT cytogenetic population will include all patients who are randomized and have a cytogenetic assessment at baseline with at least 20 metaphases examined, regardless of whether they take the assigned study drug. The primary analyses of cytogenetic efficacy will be based on this population. Randomized patients with at least 20 metaphases examined at baseline without response assessments will be considered as non-responders in the primary cytogenetic efficacy analyses.

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

**Per-protocol Population:** The per-protocol population includes all patients who are randomized, receive at least 1 dose of study drug, and have no major protocol violations that could be expected to impact response data (such as failure to satisfy 1 or more eligibility criteria, administration of other anti-cancer therapy concurrent with study drug, or administration of incorrect dose [e.g., starting dose that was not the one to which the patient was randomized], no post-baseline BCR-ABL$^{IS}$ assessment).

Numbers of patients in ITT, ITT cytogenetic, treated, and PP populations will be described. PP analyses are not planned for the IA. The PP analyses will only be performed at the analysis for final CSR if the difference in number of patients between ITT population and PP population is at least 5 in each cohort.

### 4.3 Patient Disposition

The following data for patient disposition will be summarized:

- Numbers of patients still on study treatment
- Numbers of patients discontinued from treatment
- Primary reason for treatment discontinuation
- Follow-up status
- Duration of follow-up

### 4.4 Major Protocol Deviations

Major protocol deviations that could be expected to impact analysis of the primary endpoint, such as: failure to satisfy one or more eligibility criteria, administration of incorrect dose (eg, starting dose that was not the one to which the patient was randomized), no baseline or post-baseline cytogenetic or molecular response assessment, administration of prohibited anti-cancer therapy concurrent with study drug, will be identified prior to database lock and will be listed and summarized.

### 4.5 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized separately for each cohort and will include at a minimum:

- Age, gender, race, ethnicity, geographic region, weight and height, ECOG score
- Time from initial diagnosis of CP-CML to first dose date (years)
- Medical history including history of hypertension, diabetes, and hyperlipidermia
- Prior TKI therapy and anti-cancer regimen
- Resistance or intolerance to prior TKIs
- Mutation status at baseline
- Cytogenetic, hematologic, and molecular statuses at baseline

### 4.6 Concomitant Medications

Prior and concomitant medications will be coded using the WHO drug dictionary. Medications not in the WHO dictionary will be summarized as 'Not Coded' for analysis. Concomitant medications (CMs) defined as all medications used on or after the first dose of study treatment will be summarized. Medications belonging to categories of interest such as aspirin and anticoagulants will be identified and summarized.

## 4.7 Efficacy Analyses

### 4.7.1 Efficacy Assessments

Efficacy assessments are described in the protocol Section 13.1 and comprise:

- BCR-ABL assessment to determine molecular response
- BM aspirates for assessment of cytogenetic response
- Complete blood count for assessment of hematologic response
- Survival follow-up
- CCI [redacted]

### 4.7.2 Definitions of Efficacy Endpoints

The primary and secondary efficacy endpoints are listed in Section 2.2. This section provides the definitions of the endpoints and the associated conditions defining loss of those endpoints.

#### *4.7.2.1 Molecular Response Definitions*

Molecular response rates will be assessed at the time points specified above in . Windows for specific time points will be defined at the end of Section 4.7.2.

**Molecular response: MR1, ≤1% BCR-ABL1$^{IS}$, MMR, MR4, and MR4.5** are defined as ≤10%, ≤1%, ≤ 0.1%, ≤ 0.01%, and ≤ 0.0032% BCR-ABL1$^{IS}$, respectively. In the case of undetectable BCR-ABL transcript levels, a minimum of 10,000 and 32,000 ABL copies must be present in order to be classified as MR4 and MR4.5, respectively measured by real-time quantitative PCR.

**Time to MR1/≤1% BCR-ABL1$^{IS}$ /MMR/MR4/MR4.5** is defined as the interval between the first dose date of the study treatment and the first date at which the criteria for MR1/≤1% BCR-ABL1$^{IS}$/MMR/MR4/MR4.5 are met.

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

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

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

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

**Duration of ≤1% BCR-ABL$^{IS}$/MMR/MR4/MR4.5** is defined as the interval between the first assessment at which the criteria for MR1/≤1% BCR-ABL$^{IS}$/MMR/MR4/MR4.5are met until the earliest date at which loss of MR1/≤1% BCR-ABL$^{IS}$/MMR/MR4/MR4.5occurs (as defined above), or the criteria for progression (Section 4.7.2.4) are met. Patients remaining in MR1/≤1% BCR-ABL$^{IS}$/MMR/MR4/MR4.5will be censored at the last date at which the criteria for MR1/≤1% BCR-ABL$^{IS}$/MMR/MR4/MR4.5are met.

#### *4.7.2.2 Cytogenetic Response Definitions*

**Rate of MCyR at 12 months** is the proportion of patients achieving CCyR or PCyR at 12 months (with a time window as defined at the end of Section 4.7.2) after initiation of study drug Cytogenetic response is the percentage of Ph+ metaphases in bone marrow (peripheral blood may not be used), based on a review of a minimum of 20 metaphases. Responses are defined as follows:

Major cytogenetic response (MCyR): CCyR or PCyR

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

Each patient's best response will be chosen according to the order of: CCyR, PCyR, less than PCyR, not evaluable. Per schedule of events in the protocol, cytogenetic data is collected at month 12 and end of treatment, therefore, MCyR and CCyR data will be analyzed at month 12 and by the end of treatment.

**Rate of CCyR at 12 months** is the proportion of patients achieving CCyR at 12 months (with a time window as defined at the end of Section 4.7.2).

#### *4.7.2.3 Hematologic Response Definitions*

**CHR** is defined as achieving *all* of the following measurements:

- White blood cells (WBC) ≤ institutional ULN
- Platelets < 450,000/$mm^3$
- No blasts or promyelocytes in peripheral blood
- < 5% myelocytes plus metamyelocytes in peripheral blood
- Basophils in peripheral blood < 5%
- No extramedullary involvement (including no hepatomegaly or splenomegaly)

**Loss of CHR** is defined as the appearance of any of the following, confirmed by a second assessment at least 4 weeks later (unless associated with progression [Section 4.7.2.4] or CML-related death):

- WBC count that rises to > 20,000/$mm^3$
- Platelet count that rises to ≥ 600,000/$mm^3$
- Splenomegaly progressing to a size ≥ 5 cm below the left costal margin
- Appearance of ≥ 5% myelocytes plus metamyelocytes in peripheral blood
- Appearance of blasts or promyelocytes in the peripheral blood

#### *4.7.2.4 Event-Related Definitions*

**PFS** is defined as the interval between the first dose date of study treatment and the first date at which the criteria for **progression** are met (progression to the accelerated phase or blast phase of CML), or death due to any cause, censored at the last response assessment.

**Progression to AP** is defined as:

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

  **or**

- ≥ 20% basophils in peripheral blood or bone marrow

  **or**

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

  **or**

- < $100 \times 10^9$ platelets/L in peripheral blood unrelated to therapy

  **or**

- Cytogenetic, genetic evidence of clonal evolution

  **and**

- No extramedullary disease

**Progression to BP** is defined as:

- ≥ 30% blasts in peripheral blood or bone marrow

  **or**

- Extramedullary disease other than hepatosplenomegaly

PFS will also be analyzed according to the criteria in O'Brien et al, 2003:

1. Death
3. Development of AP or BP
4. Loss of CHR (in the absence of cytogenetic response)
   Confirmed by development in complete blood counts (CBCs) at least 4 weeks apart
5. Loss of MCyR by BM cytogenetic assessment
6. Increasing WBC in patient without CHR defined by:
   Doubling of WBC to >20K on 2 occasions at least 4 weeks apart (after the first 4 weeks of therapy)

**OS** is defined as the interval between the first dose date of study treatment and death due to any cause, censored at the last contact date when the patient was alive.

#### *4.7.2.5 Time Windows for Analyses of Molecular and Cytogenetic Response*

**Table 1 Time Windows for Analyses of Molecular Response[1]**

| Planned Assessment[2] | Time window |
|---|---|
| Baseline | As specified in |
| Month 3 (Day 84) | Day 42 – Day 126 |
| Month 6 (Day 168) | Day 127 – Day 210 |
| Month 9 (Day 252) | Day 211 – Day 294 |
| Month 12 (Day 336) | Day 295 – Day 378 |

[1]Molecular response assessed at Month 1, 2, 3 and every 3 months thereafter.
[2]Planned Assessments beyond Month 12 will be determined in a similar fashion.

**Table 2 Time Windows for Analyses of Cytogenetic Response**

| Planned Assessment | Time window |
|---|---|
| Baseline | As specified in |
| Month 12 (Day 336) | Day 253 – Day 420 |



### 4.7.3 Primary Endpoint Analysis

The primary analysis of the primary endpoint for each cohort is based on the ≤1% BCR-ABL$^{IS}$rate at 12 months. The 2-sided type I error adjusted for the 3 statistical tests, using the Bonferroni method, will be set at 0.05/3=0.0167. Analysis of ≤1% BCR-ABL$^{IS}$ rate will be performed using a 2-sided 98.3% exact CI. The point estimate of ≤1% BCR-ABL$^{IS}$ rate and a 98.3% exact CI, based on the exact binomial distribution (Clopper-Pearson exact CI), will be presented. Ponatinib will be considered promising if the lower limit of 2-sided 98.3% exact CI for the ≤1% BCR-ABL$^{IS}$ rate exceeds 20%. A 2-sided exact 95% CI will also be provided.
The primary analysis population for the primary efficacy endpoint will be based on the ITT population. The analysis for the primary endpoint will also be performed using the per-protocol population for the final CSR when the difference in number of patients between ITT population and PP population is at least 5 in each cohort.

The primary analysis for the proportion of patients achieving ≤ 1% BCR-ABL1$^{IS}$ at 12 months will:

- include all ITT patients who have been on study for up to 12 months, including the following defined as failure
    - any patient with early termination before 12 months
    - any patient with no molecular assessment performed at 12 months
    - any patient with molecular assessment results not available at 12 months
    - any patient with baseline molecular assessment results ≤ 1% BCR-ABL1$^{IS}$

- Patients who are ongoing in the study but have not achieved 12 months time point since they were randomized in the study will be excluded in the analyses

Based on ITT population, the following sensitivity analyses on the primary endpoint will be conducted:

1. Patients with MR2 (≤ 1% BCR-ABL1$^{IS}$) at baseline will be considered as failure or success based on the results at 12 months
2. Patients with MR2 (≤ 1% BCR-ABL1$^{IS}$) at baseline will be excluded

In the sensitivity efficacy analyses using the Safety population, failure is defined as

- Patients with atypical transcript
- Patients who have b2a2/b3a2 transcript type without response assessments, including
  - any patient with early termination before 12 months
  - any patient with no molecular assessment performed at 12 months
  - any patient with molecular assessment results not available at 12 months

Patients who are ongoing in the study but have not achieved 12 months time point since they were randomized in the study will be excluded in the analyses

Specifically, the following sensitivity analyses based on safety population will be conducted:

1. Patients with MR2 (≤ 1% BCR-ABL1$^{IS}$) at baseline will be considered as failure regardless of the results at 12 months
2. Patients with MR2 (≤ 1% BCR-ABL1$^{IS}$) at baseline will be considered as failure or success based on the results at 12 months
3. Patients with MR2 (≤ 1% BCR-ABL1$^{IS}$) at baseline will be excluded

#### *4.7.3.1 Data Handling Rules for the Primary Analyses of the Primary Endpoint*

The following rules will be implemented for the primary analysis of ≤1% BCR-ABL$^{IS}$ at 12 months in CP-CML patients:

- Patients will be excluded from the analysis if they meet any of the following criteria (consistent with the ITT population definition above):
  - Do not have the b2a2/b3a2 variable of BCR-ABL
- Patients will be considered as non-responders if they meet any of the following criteria:
  - Are randomized but untreated
  - Do not respond at 12 months after the initiation of study treatment
  - Undergo no baseline PCR assessment
  - Have ≤1% BCR-ABLIS at baseline
- If a response evaluation is missing for the 12 month time point, but the criteria for ≤1% BCR-ABL$^{IS}$ have been met at the 9 month and 15 month time points, then the missing 12 month time point will be imputed as having met the criteria for ≤1% BCR-ABL$^{IS}$.

### 4.7.4 Secondary Efficacy Endpoint Analyses

#### *4.7.4.1 Secondary Efficacy Endpoints*

They analyses of secondary molecular efficacy endpoints will be performed on the ITT population. The analyses of secondary cytogenetic efficacy endpoints will be performed on the ITT cytogenetic population. The analyses of secondary endpoints may also be performed on the per-protocol population. The analyses of time to event and duration of response will be conducted for each dose cohort, and for descriptive purposes only.

- MMR at 12 months; MMR at 24 months. Number and percent of patients with the response will be summarized. Ninety-five percent exact CI for the response rate will be calculated.
- MCyR at 12 months. Number and percent of patients with the response will be summarized. Ninety-five percent exact CI for the response rate will be calculated.
- Duration of MMR in responders only. Kaplan-Meier method will be used to estimate duration of response among patients meeting the criteria for MMR. Median duration of response in days and the 95% CI will be provided.
- CCyR at 12 months. Number and percent of patients with the response will be summarized. Ninety-five percent exact CI for the response rate will be calculated.
- PCyR at 12 months. Number and percent of patients with the response will be summarized.
- MR1 (≤ 10% BCR-ABL$^{IS}$) at 3 months and, MMR, MR4, and MR4.5 at and by 3-month intervals other than the time points specified above (time window as specified at the end of . Number and percent of patients with the responses will be summarized at the protocol scheduled molecular assessment visits. Ninety-five percent exact CIs will be calculated
- ≤1% BCR-ABL$^{IS}$ by 12 months, and at and by 6, 18 and 24 months (time window as specified at the end of Number and percent of patients with the responses will be summarized. Ninety-five percent exact CIs will be calculated
- MMR, MR4, and MR4.5 at any time after initiation of study treatment. Number and percent of patients with the responses will be summarized. Ninety-five percent exact CIs will be calculated.
- CHR at any time and CHR at 3 months (between 42 and 126 days after the initiation of treatment). Number and percent of patients with the responses will be summarized. Ninety-five percent exact CIs will be calculated for CHR rate at any time.
- Time to ≤1% BCR-ABL$^{IS}$, MMR, MR4, and MR4.5. Median times to response in days, minimum, and maximum values will be provided for patients who are responders.
- Duration of ≤1% BCR-ABL$^{IS}$ in responders only. Kaplan-Meier method will be used to estimate duration of response among patients meeting the criteria for ≤1% BCR-ABL$^{IS}$. Median duration of response in days and the 95% CI will be provided.
- Rate of progression to AP- or BP-CML. Number and percent of patients who have progressed to AP or BP based on the criteria in will be provided.

- PFS will be estimated using Kaplan-Meier method. Median time to event in days and its 95% CI will be provided.
- OS will be estimated using Kaplan-Meier method. Median time to event in days and its 95% CI will be provided.

#### *4.7.4.2 Data Handling Rules for Secondary Efficacy Endpoint Analyses*

The following rules will be implemented for the primary analysis of MCyR at 12 months in CP-CML patients:

- Patients will be excluded from the analysis if they meet any of the following criteria (consistent with the ITT cytogenetic population as defined above):
    - Have fewer than 20 metaphases examined at baseline
    - Are in CCyR at baseline
    - Undergo no baseline cytogenetic assessment
- Patients will be considered as non-responders if they meet any of the following criteria:
    - Any patient with early termination before 12 months
    - Are randomized but untreated
    - Do not respond at 12 months after the initiation of study treatment
    - Have missing results or assessment not performed
- Patients who meet the criteria for PCyR at baseline must achieve CCyR after baseline in order to be considered as meeting the criteria for MCyR.
- Patients who are ongoing in the study but have not achieved 12 months time point since they were randomized in the study will be excluded in the analyses.
- At any given cytogenetic assessment after baseline, if fewer than 20 metaphases are examined, the following rule will apply to the determination of MCyR:

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

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

The following rules will be implemented for the primary analysis of CCyR at 12 months in CP-CML patients:

- Patients will be excluded from the analysis if they meet any of the following criteria (consistent with the ITT cytogenetic population as defined above):
    - Have fewer than 20 metaphases examined at baseline
    - Are in CCyR at baseline
    - Undergo no baseline cytogenetic assessment
- Patients will be considered as nonresponders if they meet any of the following criteria:
    - Any patient with early termination before 12 months
    - Are randomized but untreated
    - Do not respond at 12 months after the initiation of study treatment
    - Have missing results or assessment not performed
- Determination of CCyR will require at least 20 metaphases examined.
- Patients who are ongoing in the study but have not achieved 12 months time point since they were randomized in the study will be excluded in the analyses

For the primary analysis of the molecular secondary efficacy endpoints, the following data handling rule will be used:

- Patients will be excluded from the analysis if they meet any of the following criteria (consistent with the ITT population as defined above):
    - Do not have the b2a2/b3a2 variable of BCR-ABL
    - Meet the criteria at baseline for the specific response being analyzed (i.e. for the analysis of MMR, patients who meet the criteria for MMR at baseline will be excluded)
    - Undergo no baseline BCR-ABL$^{IS}$ measurement
- Patients will be considered as non-responders if they meet any of the following criteria:
    - Are randomized but untreated
    - Do not have a post-baseline assessment
- The initial determination of CHR requires CBC with differential and physical exam, and the 2 assessments must be performed within 14 days of one another. At assessments subsequent to the assessment at which the criteria for CHR are first met, a physical exam is not required. Patients with CHR at baseline will be considered as nonresponders. Patients with no post-baseline hematologic assessments will be considered as nonresponders.

- For CBC with differential, if the sum of the percentages of the reported cell types of the differential was at least 98%, all other cell types not reported in the differential were assumed to be 0.

- For the secondary endpoints of MCyR, CCyR, CHR, MR1, MMR, MR4, and MR4.5 at specific timepoints, if a response evaluation is missing for a specific timepoint, but the criteria for response have been met at the protocol-scheduled timepoints immediately before and after, then the missing timepoint will be imputed as having met the criteria for response. Additionally, any patient with early termination before the time point being analyzed will be classified as failure.

### 4.7.5 Additional Exploratory Efficacy Endpoint Analyses

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### 4.7.6 Subgroup Analyses of the Primary Endpoint and Secondary Efficacy Endpoints

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

- Age (< 60 years, ≥ 60 years)
- History of hypertension, diabetes, and/or hyperlipidemia (Yes, No)
- Gender (Male, Female)
- Race (White, Black or African American, Asian, Other)
- Geographic region (North/South America, Europe/Australia, Asian)
- T315I at baseline (Yes, No)
- Number of prior approved TKI therapies (imatinib, dasatinib, nilotinib, bosutinib for 2, 3, 4 TKIs)
- Other disease-related prognostic factors

## 4.8 Safety Analysis

All patients receiving at least 1 dose of study drug will be considered evaluable for safety. Safety analyses will be performed based on the treated population. All AEs with an initial onset date on or after the first dose date, and no later than 30 days after the last dose date of study treatment (or events starting after initial consent that worsen in severity on or after the first dose date) will be considered

treatment-emergent. Rates of AEs and SAEs will be summarized for treatment-emergent events (TEAEs), and all AEs will be listed.

### 4.8.1 Analysis of AOEs and VTEs

Arterial occlusive and venous thromboembolic events with an initial onset date on or after the first dose date will be considered treatment-emergent and summarized. Number and percentages of patients who developed AOEs and VTEs will be summarized for each cohort. These events will be categorized as follows:

- Arterial occlusive events
    - Cardiovascular occlusive events
    - Cerebrovascular occlusive events
    - Peripheral vascular occlusive events
    - Arterial unclassified
- Venous thrombotic events
- Vascular unclassified

Exposure-adjusted incidence rates (EAIR) of AOEs and VTEs will be calculated for each cohort and for all patients. The EAIR is calculated as number of patients with the AE divided by total treatment exposure time $\sum t_i$, $t_i$ is a patient's exposure time. For patients with events, $t_i$ is the time from the first dose date to the first onset date of the event. For patients without an event, $t_i$ is the time from the first dose date to the last dose date. The exact 95% CI of the EAIR will be computed (Ulm, 1990).

The following additional descriptive analyses will be performed to characterize AOEs and VTEs, and will be calculated separately for each of the categories described above:

- **Time to onset**: Calculated as date of first event AE- first dose date + 1
- **Dose at onset**: Dose of ponatinib taken immediately prior to onset of first event

Baseline risk factors and other relevant baseline characteristics for the occurrence of AOEs will be evaluated for all patients, and will include:

- History of ischemic disease
- History of nonischemic cardiac disease
- Hypertension
- History of diabetes
- History of smoking (current smoker, former smoker, never smoker)
- Obesity (history of obesity or baseline BMI $\geq$30 kg/m$^2$)
- History of hypercholesterolaemia
- Age
- Gender
- Other risk factors

### 4.8.2 Analysis of Categories of AEs

Categories of AEs will be prospectively defined using Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs) or Modified MedDRA Queries based on SMQs and MedDRA System Organ Classes (SOCs). The AE crude rates, as well as the frequency of occurrence by overall toxicity—categorized by toxicity grades (severity)—will be described for each cohort. Events will also be characterized by time to onset, dose at onset, and duration, as described above. Categories of AEs will include but will not be limited to:

- Cardiac failure
- Arrhythmias including QT prolongation
- Pancreatitis and Amylase or Lipase elevations
- Hepatotoxicity
- Myelosuppression
- Hemorrhage
- Fluid retention
- Hypertension

### 4.8.3 TEAEs, Treatment-Related AEs and SAEs

For all TEAEs, treatment-emergent treatment-related AEs and SAEs, crude rates—as well as the frequency of occurrence by overall toxicity, categorized by toxicity grades (severity)—will be described for each cohort.

### 4.8.4 Analyses of Treatment Discontinuation Rate due to AEs, Dose Reductions, and Dose Interruptions

Tolerability will be summarized by:

- Rate of treatment discontinuation due to AEs in each dose cohort
- Dose reductions in each dose cohort. Dose reduction is defined as any dose reduction due to AE, excluding the mandatory dose reduction described in the protocol Section 14.1.3.
- Dose interruptions in each dose cohort. Dose interruption is defined as at least 3 consecutive days gap with no dose taken due to AE.

Number of days on the starting dose and on reduced dose(s) will be summarized in order to characterize length of dose interruptions and reductions due to AE. Number of patients with dose interruption without resuming dosing after the interruption will be provided.

### 4.8.5 Study Drug Exposure

Parameters pertaining to study drug exposure (ie, duration of exposure, number of days dosed, dose intensity, total cumulative dose) will be summarized separately for each cohort. Duration of treatment exposure is defined as the time interval from the first dose to the last dose of study treatment (last dose date – first dose date +1). Dose intensity in mg/day is calculated as total cumulative dose in mg divided by duration of treatment exposure in day.
In addition, the following data will be summarized:

- Number of patients in cohorts A and B who have dose reduction to 15 mg after achieving ≤1% BCR-ABL$^{IS}$

- Number of patients who re-escalate dose after loss of ≤1% BCR-ABL$^{IS}$

### 4.8.6 Laboratory Tests

Listings of laboratory test results will be generated, and shifts in laboratory parameters from baseline to the worst value occurring after first dose date and up to last dose date + 30 days (in terms of NCI CTCAE, v.4.0 grades) will be summarized.

### 4.8.7 Blood Pressures

Shift from baseline to the maximum value occurring after first dose date and up to last dose date + 30 days in systolic and diastolic blood pressures and mean change from baseline over time will be summarized.

### 4.8.8 ECG and ECHO

QTcF will be calculated and shift from baseline to the maximum value occurring after first dose date and up to last dose date + 30 days will be summarized. Summaries of left ventricular ejection fraction at baseline and shift from baseline to the minimum value occurring after first dose date and up to last dose date + 30 days will be provided.

## 4.9 Exposure-Response Analysis

Analyses of the relationship between steady-state plasma ponatinib exposure and efficacy (MCyR, ≤1% BCR-ABL$^{IS}$, and MMR) and safety measures (including, at a minimum, AOEs, VTEs, and events occurring in at least 30 patients in at least one treatment group), will be undertaken. Logistic regression models and Cox regression models will be used for the binary outcomes, with exposure as a time varying covariates. The results of the analyses will be provided in a separate report.

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## 5 REFERENCES

Ulm K. A simple method to calculate the confidence interval of a standardized mortality ratio. American Journal of Epidemiology 1990; 131(2): 373-375.

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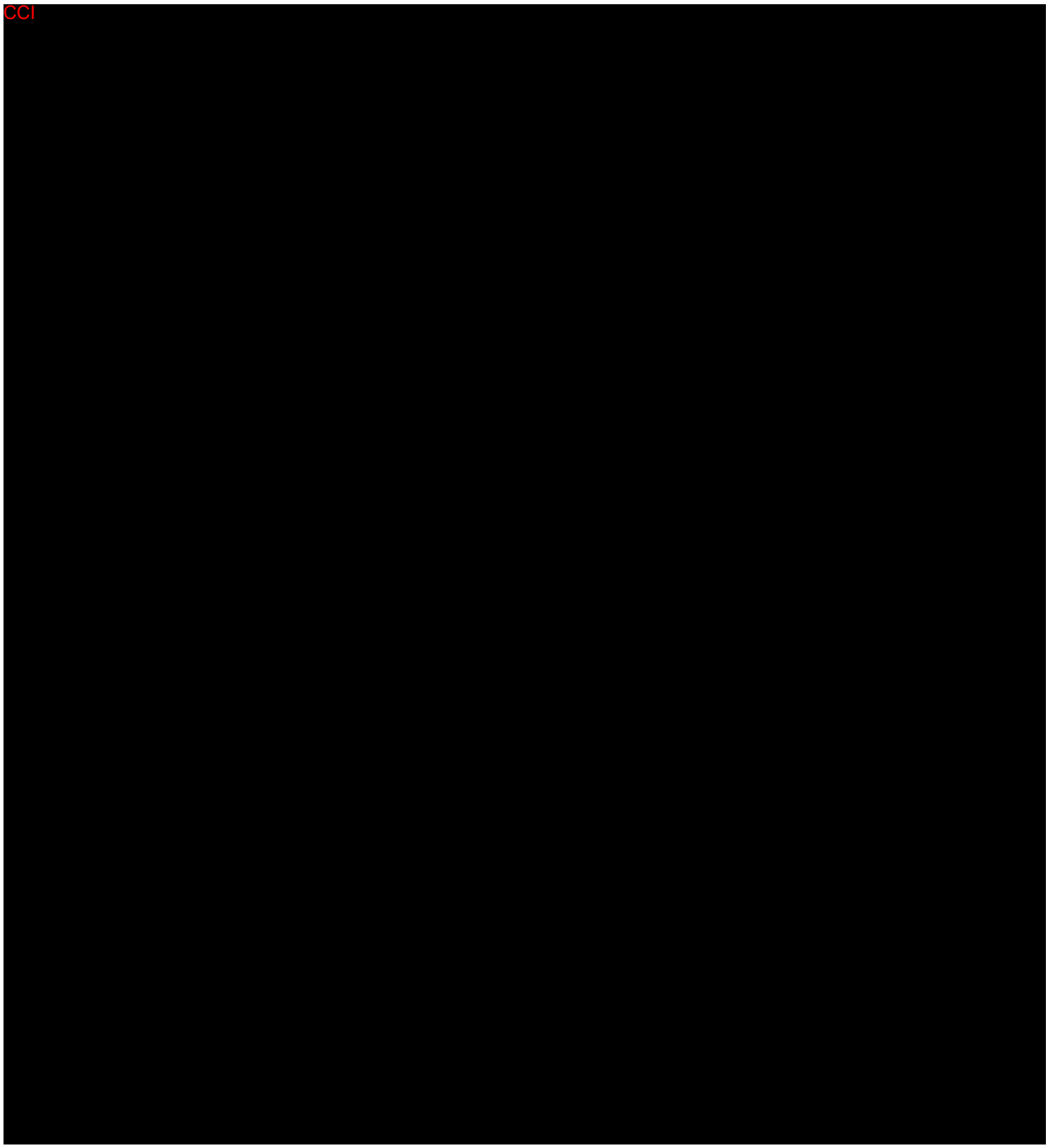
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*For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on-line at www.facit.org.