Statistical Analysis Plan

NCT Number: NCT02467270

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

Study Number: AP24534-14-203

Document Version and Date: Version 3.0, 28 Jun 2024 and Version 4.0, 13 May 2025

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

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: **078,375**

SPONSOR: Takeda Development Center Americas, Inc.

95 Hayden Avenue

Lexington, MA 02421

USA

617-349-0200

Note: Takeda Development Center Americas, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "sponsor," or "Takeda."

VERSION 3.0

DATE: 28 JUNE 2024

Prepared by:

[redacted], PhD

[redacted], Oncology Statistics

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
Protocol Amd 5.0	2.2	16 December 2019
Protocol Amd 7.0	3.0	28 June 2024

Approval Signatures

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

Approvals:

[redacted], PhD
[redacted], Oncology Statistics

Date

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

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
EQ	EuroQol
EWB	emotional well-being
FACT-G	Functional Assessment of Cancer Therapy - General
FACT-Leu	Functional Assessment of Cancer Therapy – Leukemia
FWB	functional well-being
HR-QoL	health-related quality of life
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
Ph+	Philadelphia chromosome positive
PK	pharmacokinetic(s)
PP	per-protocol
PWB	physical well-being
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
SWB	social well-being
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

1.0 INTRODUCTION

This Statistical Analysis Plan (SAP) 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 7.0.

This SAP amendment V3.0 also provides guidance for OPTIC 5-year data analysis focusing on long term efficacy and safety data and the results will be reported in the CSR amendment. For short term endpoints (for example: molecular response at 12 month, etc.), if analysis had been done and reported in the primary analysis CSR, then no repeat results will be generated based on OPTIC 5 year data.

2.0 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) by 12 months and 24 months and rate of major cytogenetic response (MCyR) by 12 months
- To evaluate duration of MMR
- To characterize the rates of arterial occlusive events (AOEs), venous thromboembolic events (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

- Correlation of tumor cell and plasma biomarkers with ponatinib efficacy and safety.
- Quality of Life (QoL) and health outcomes.

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

- Correlation of tumor cell and plasma biomarkers with ponatinib efficacy and safety
- QoL and health outcomes as measured by EQ-5D-5L and FACT-Leu

3.0 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 16.5.1.1 of 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 15 mg 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 intent-to-treat (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).

4.0 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 (ie, 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 (PP) 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 [eg, 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 hyperlipidemia
- 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
- QoL and health outcomes as measured by EQ-5D-5L and FACT-Leu

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 Section 2.2. Windows for specific time points will be defined in Section 4.7.2.5.

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/MR4.5 are met until the earliest date at which loss of MR1/≤1% BCR-ABL^{IS}/MMR/MR4/MR4.5 occurs (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/MR4.5 will be censored at the last date at which the criteria for MR1/≤1% BCR-ABL^{IS}/MMR/MR4/MR4.5 are 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 in Section 4.7.2.5) 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 in Section 4.7.2.5).

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

- < 100×10^9 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
2. Development of AP or BP
3. Loss of CHR (in the absence of cytogenetic response)

   Confirmed by development in complete blood counts (CBCs) at least 4 weeks apart
4. Loss of MCyR by BM cytogenetic assessment
5. Increasing WBC in patient without CHR defined by:

   Doubling of WBC to >20K on 2 occasions at least 4 weeks apart (after the first 4 weeks of therapy)

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 4.a Time Windows for Analyses of Molecular Response[1]

Planned Assessment[2]	Time window
Baseline	As specified in Section 4.1
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 4.b Time Windows for Analyses of Cytogenetic Response

Planned Assessment	Time window
Baseline	As specified in Section 4.1
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 month 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 month 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

The analyses of secondary molecular efficacy endpoints may 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 may 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 and by 3-month intervals other than the time points specified above (time window as specified in Section 4.7.2.5). 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, 24, 36, 48, 60 months (time window as specified in Section 4.7.2.5. 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. 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 Section 4.7.2.4 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 secondary analysis of MCyR at/by 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 month 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 month time point since they were randomized in the study will be excluded in the analyses

For the 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
  - 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
  - Meet the criteria for molecular response at baseline for a specific response
- 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 MR1, MMR at 12 months, if a response evaluation is missing, but the criteria for response have been met at the protocol-scheduled immediately before and after (ie, at 9 months and 15 months), 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

The additional analyses of exploratory efficacy endpoints may be performed on the ITT population.

- Concordance of ≤1% BCR-ABL^{IS} and CCyR and MCyR by 12 months. At 12 months BM cytogenetic assessment and molecular response assessment in peripheral blood will be performed. Cross tabulation of ≤1% BCR-ABL^{IS} by CCyR and by MCyR will be provided, respectively.

- Concordance of MR1 and MCyR by 12 months. At 12 months BM cytogenetic assessment and molecular response assessment in peripheral blood will be performed. Cross tabulation of MR1 by MCyR will be provided.

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

For the primary endpoint and key secondary efficacy endpoints, subgroup analyses by age (<65 years vs ≥65 years) will also be performed.

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 toxicity grade) 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% $BCR\text{-}ABL^{IS}$, 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 were provided in a separate report.

4.10 QoL/Health Outcomes Analysis

QoL and health outcomes measures will be collected using the EQ-5D-5L and FACT-Leu instruments. Means and medians of scores of these questionnaires will be summarized for each dose cohort by time point, overall, and for each domain.

4.10.1 EQ-5D-5L

The EQ-5D-5L questionnaire is a validated, self-administered general questionnaire of health-related quality of life (HR-QoL) issues, developed by EuroQoL Group. The questionnaire asks patients to rate their HR-QoL for 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The instrument contains a descriptive element—with patients being asked to rate each dimension on a 5-level descriptive severity scale (no problem, slight, moderate, severe, and extreme problems)—and a visual analog scale from 0 to 100 with 100 being best health. Number and percent of patients in the 5 levels will be presented for each cohort. Mean scores for the VAS will be calculated.

4.10.2 FACT-Leu

The FACT-Leu questionnaire is a validated, self-administered questionnaire of HR-QoL, developed specifically for patients with leukemia. The questionnaire contains items divided into 4 QoL domains: physical well-being, social/family well-being, emotional well-being, and functional well-being. A fifth category "Additional Concerns" contains general questions. There are 5 responses for each item with the score assigned: 0=Not at all, 1= A little bit, 2=Somewhat, 3=Quite a bit, 4=Very much. The scoring method is provided in Appendix 1. The higher the scores, the better the QoL. The subscale scores, FACT-Leukemia TOI score, FACT-G total score, and FACT-Leukemia total score will be summarized by visit.

4.11 Exploratory Biomarker Analyses

The mutation status of BCR-ABL and other genes implicated in tumor biology and/or drug metabolism will be determined through analyses of tumor cells collected at study entry, on study, and/or at End-of-Treatment. Analysis methodologies include, but are not limited to, DNA sequencing, digital PCR, and mass spectrometry. Plasma samples collected at study entry, on study, and at End-of-Treatment may be assessed for circulating biomarkers (eg, cytokines, chemokines, and growth factors) to identify associations with ponatinib efficacy and safety.

4.12 Changes in the Statistical Analysis Plan

Reference materials for this statistical analysis plan include Clinical Study Protocol AP24534-14-203 Amendment 7 (Protocol Amendment dated 07 April 2021). This SAP amendment version 3.0 also provides guidance for OPTIC 5 year data analysis focusing on long term efficacy and safety data and the results will be reported in the CSR amendment. For short term endpoints (for example: molecular response at 12 month, etc.), if analysis had been done and reported in the primary analysis CSR, then no repeat results will be generated based on OPTIC 5 year data. Additional major changes include:

- Added the primary endpoint and key secondary efficacy endpoint analysis by subgroup of age category (<65 years vs >=65 years)
- Clarified imputation rule for the analysis of molecular response at 12 month and clarified data handling rules for the analysis of molecular secondary endpoints
- Removed analysis for time to MR4.5
- Removed the laboratory toxicity grading version specification as both version 4.03 and version 5.0 are implemented if the grading criteria is not available in version 5.0.

5.0 REFERENCES

O'Brien, S. G., Guilhot, F., Larson, R. A., Gathmann, I., Baccarani, M., Cervantes, F., et al. 2003. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med,* 348(11), 994-1004.

Ulm, K. 1990. A simple method to calculate the confidence interval of a standardized mortality ratio (SMR). *Am J Epidemiol,* 131(2), 373-5.

6.0 APPENDIX 1

FACT-Leukemia Scoring Guidelines (Version 4) – Page 1

Instructions:* 1. Record answers in "item response" column. If missing, mark with an X

2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. Add subscale scores to derive total scores (TOI, FACT-G & FACT-Leukemia).
5. **The higher the score, the better the QOL.**

Subscale	Item Code	Reverse item?		Item response	Item Score
PHYSICAL	GP1	4	-	_____	=_____
WELL-BEING	GP2	4	-	_____	=_____
(PWB)	GP3	4	-	_____	=_____
	GP4	4	-	_____	=_____
Score range: 0-28	GP5	4	-	_____	=_____
	GP6	4	-	_____	=_____
	GP7	4	-	_____	=_____

Sum individual item scores: _____

Multiply by 7: _____

Divide by number of items answered: _____=**PWB subscale score**

SOCIAL/FAMILY	GS1	0	+	_____	=_____
WELL-BEING	GS2	0	+	_____	=_____
(SWB)	GS3	0	+	_____	=_____
	GS4	0	+	_____	=_____
Score range: 0-28	GS5	0	+	_____	=_____
	GS6	0	+	_____	=_____
	GS7	0	+	_____	=_____

Sum individual item scores: _____

Multiply by 7: _____

Divide by number of items answered: _____=**SWB subscale score**

EMOTIONAL	GE1	4	-	_____	=_____

WELL-BEING	GE2	0	+	_____	=_____
(EWB)	GE3	4	-	_____	=_____
	GE4	4	-	_____	=_____
Score range: 0-24	GE5	4	-	_____	=_____
	GE6	4	-	_____	=_____

Sum individual item scores: _____

Multiply by 6: _____

Divide by number of items answered: _____=**EWB subscale score**

FUNCTIONAL	GF1	0	+	_____	=_____
WELL-BEING	GF2	0	+	_____	=_____
(FWB)	GF3	0	+	_____	=_____
	GF4	0	+	_____	=_____
Score range: 0-28	GF5	0	+	_____	=_____
	GF6	0	+	_____	=_____
	GF7	0	+	_____	=_____

Sum individual item scores: _____

Multiply by 7: _____

Divide by number of items answered: _____=**FWB subscale score**

FACT-Leukemia Scoring Guidelines (Version 4) – Page 2

Subscale	**Item Code**	**Reverse item?**		**Item response**	**Item Score**
LEUKEMIA	BRM3	4	-	_____	=_____
SUBSCALE	P2	4	-	_____	=_____
(LEUS)	BRM2	4	-	_____	=_____
	ES3	4	-	_____	=_____
Score range: 0-68	LEU1	4	-	_____	=_____
	TH1	4	-	_____	=_____
	TH2	4	-	_____	=_____
	HI12	4	-	_____	=_____
	BMT6	4	-	_____	=_____
	C2	4	-	_____	=_____

C6	0	+	_____	=_____
An7	0	+	_____	=_____
N3	4	-	_____	=_____
LEU5	4	-	_____	=_____
LEU6	4	-	_____	=_____
BRM9	4	-	_____	=_____
LEU7	4	-	_____	=_____

Sum individual item scores:_____

Multiply by 17: _____

Divide by number of items answered: _____**=LEU Subscale score**

To derive a FACT-Leukemia Trial Outcome Index (TOI):
Score range: 0-124

_____ + _____ + _____ =_____**=FACT-Leukemia TOI**
(**PWB** score) (**FWB** score) (**LeuS** score)

To Derive a FACT-G total score:
Score range: 0-108

_____ + _____ + _____ + _____=_____**=FACT-G Total score**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score)

To Derive a FACT-Leukemia total score:
Score range: 0-176

_____ + _____ + _____ + _____ + _____ =_____**=FACT-Leukemia Total score**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score) (**LeuS** score)

*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.

7.0 APPENDIX 2

Table Shells for the Primary and Sensitivity Analysis of the Primary Endpoint

Table 25.2.1.1
Primary Analysis of Molecular Response Assessment by Treatment Arm[1]
ITT Population[2]

Time Point		COHORT A (45 MG) (N=xx)	COHORT B (30 MG) (N=xx)	COHORT C (15 MG) (N=xx)
Month 12	BCR-ABL^{IS} Ratio n (%)			
	n	XX	XX	XX
	> 10%	XX (XX.X)	XX (XX.X)	XX (XX.X)
	<=10% (MR1)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	<=1% (MR2)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	<=0.1% (MR3)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Early Termination[3]	XX (XX.X)	XX (XX.X)	XX (XX.X)
	On Study but No BCR-ABL^{IS} Result	X (XX.X)	X (XX.X)	X (XX.X)
	Baseline MR2 or Better	X (XX.X)	X (XX.X)	X (XX.X)
	On Study but Not Achieved 12 months Time Point Since Randomized [4]	XX	XX	XX
	MR2 (<=1% BCR-ABL ^{IS}) Rate (98.3% CI)[5]	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)

Time Point	COHORT A (45 MG) (N=xx)	COHORT B (30 MG) (N=xx)	COHORT C (15 MG) (N=xx)

Note: MR1 = Molecular response with 1-log reduction; MR2 = Molecular response with 2-log reduction; MR3 = Molecular response with 3-log reduction. BCR-ABLIS = BCR-ABL1 transcript level as measured by the International Scale. Patients are grouped by their planned treatment arm.
[1] The analysis includes all ITT patients who have been on study for up to 12 months, including the following defined as failure: a) any patient with EOT/ET before 12 months, b) any patient with no molecular assessment performed or with no molecular assessment results at 12 months, and c) any patient with MR2 or better molecular assessment results (≤ 1% BCR-ABL1^{IS}) at baseline

[2] ITT population include all patients who are randomized and for whom BCR-ABL1^{IS} can be measured (ie, patients who have the b2a2/b3a2 transcript type), regardless of whether they receive the assigned study drug.

[3] EOT/ET = Discontinued treatment/early termination before 12 months.
[4] Patients who are on study but not achieved 12 month time point since randomized in the study are excluded from denominator. All other categories are included in the denominator.
[5] The 2-sided type I error rate adjusted for the three statistical tests, using the Bonferroni method, is set at 0.05/3=0.0167. The 98.3% confidence interval is calculated using the binomial exact (Clopper-Pearson) method.

Table 25.2.1.2
Sensitivity Analysis 1 of Molecular Response Assessment by Treatment Arm[1]
ITT Population[2]

Time Point		COHORT A (45 MG) (N=xx)	COHORT B (30 MG) (N=xx)	COHORT C (15 MG) (N=xx)
Month 12	BCR-ABL^{IS} Ratio n (%)			
	n	XX	XX	XX
	> 10%	XX (XX.X)	XX (XX.X)	XX (XX.X)
	<=10% (MR1)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	<=1% (MR2)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	<=0.1% (MR3)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Early Termination[3]	XX (XX.X)	XX (XX.X)	XX (XX.X)
	On Study but No BCR-ABL^{IS} Result	XX (XX.X)	X (XX.X)	X (XX.X)
	On Study but Not Achieved 12 month Time Point Since Randomized [4]	XX	XX	XX
	MR2 (<=1% BCR-ABL ^{IS}) Rate (98.3% CI)[5]	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)

Time Point	COHORT A (45 MG) (N=xx)	COHORT B (30 MG) (N=xx)	COHORT C (15 MG) (N=xx)

Note: MR1 = Molecular response with 1-log reduction; MR2 = Molecular response with 2-log reduction; MR3 = Molecular response with 3-log reduction. BCR-ABLIS = BCR-ABL1 transcript level as measured by the International Scale. Patients are grouped by their planned treatment arm.

[1] This sensitivity analysis includes all ITT patients who have been on study for up to 12 months, including the following defined as failure: a) any patient with EOT/ET before 12 months, and b) any patient with no molecular assessment performed or with no molecular assessment results at 12 months. Patients with MR2 or better molecular assessment results (≤ 1% BCR-ABL1^{IS}) at baseline will be considered as failure or success based on the results at 12 months.

[2] ITT population include all patients who are randomized and for whom BCR-ABL1^{IS} can be measured (ie, patients who have the b2a2/b3a2 transcript type), regardless of whether they receive the assigned study drug.

[3] EOT/ET = Discontinued treatment/early termination before 12 months.

[4] Patients who are on study but not achieved 12 month time point since randomized in the study are excluded from denominator. All other categories are included in the denominator.

[5] The 2-sided type I error rate adjusted for the three statistical tests, using the Bonferroni method, is set at 0.05/3=0.0167. The 98.3% confidence interval is calculated using the binomial exact (Clopper-Pearson) method.

Table 25.2.1.3
Sensitivity Analysis 2 of Molecular Response Assessment by Treatment Arm[1]
ITT Population[2]

Time Point		COHORT A (45 MG) (N=xx)	COHORT B (30 MG) (N=xx)	COHORT C (15 MG) (N=xx)
Month 12	BCR-ABL^{IS} Ratio n (%)			
	n	XX	XX	XX
	> 10%	XX (XX.X)	XX (XX.X)	XX (XX.X)
	<=10% (MR1)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	<=1% (MR2)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	<=0.1% (MR3)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Early Termination[3]	XX (XX.X)	XX (XX.X)	XX (XX.X)
	On Study but No BCR-ABL^{IS} Result	X (XX.X)	X (XX.X)	X (XX.X)
	Baseline MR2 or Better[4]	XX	XX	XX
	On Study but Not Achieved 12 month Time Point Since Randomized [4]	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
	MR2 (<=1% BCR-ABL ^{IS}) Rate (98.3% CI)[5]	XX	XX	XX

Time Point	COHORT A (45 MG) (N=xx)	COHORT B (30 MG) (N=xx)	COHORT C (15 MG) (N=xx)

Note: MR1 = Molecular response with 1-log reduction; MR2 = Molecular response with 2-log reduction; MR3 = Molecular response with 3-log reduction. BCR-ABLIS = BCR-ABL1 transcript level as measured by the International Scale. Patients are grouped by their planned treatment arm.
[1] This sensitivity analysis includes all ITT patients who have been on study for up to 12 months, including the following defined as failure: a) any patient with EOT/ET before 12 months, and b) any patient with no molecular assessment performed or with no molecular assessment results at 12 months.

[2] ITT population include all patients who are randomized and for whom BCR-ABL1^{IS} can be measured (ie, patients who have the b2a2/b3a2 transcript type), regardless of whether they receive the assigned study drug.

[3] EOT/ET = Discontinued treatment/early termination before 12 months.
[4] Patients who are on study but not achieved 12 month time point since randomized in the study or with MR2 or better molecular assessment results (≤ 1% BCR-ABL1^{IS}) at baseline are excluded from the analysis.

All other categories are included in the denominator.

[5] The 2-sided type I error rate adjusted for the three statistical tests, using the Bonferroni method, is set at 0.05/3=0.0167. The 98.3% confidence interval is calculated using the binomial exact (Clopper-Pearson) method.

Table 25.2.1.4
Sensitivity Analysis 3 Primary Analysis of Molecular Response Assessment by Treatment Arm[1]
Safety Population[2]

Time Point		COHORT A (45 MG) (N=xx)	COHORT B (30 MG) (N=xx)	COHORT C (15 MG) (N=xx)
Month 12	BCR-ABL^{IS} Ratio n (%)			
	n	XX	XX	XX
	> 10%	XX (XX.X)	XX (XX.X)	XX (XX.X)
	<=10% (MR1)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	<=1% (MR2)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	<=0.1% (MR3)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Early Termination [3]	XX (XX.X)	XX (XX.X)	XX (XX.X)
	On Study but No BCR-ABL^{IS} Result	X (XX.X)	X (XX.X)	X (XX.X)
	Baseline MR2 or Better			
		XX	XX	XX
	On Study but Not Achieved 12 month Time Point Since Randomized [4]			
		XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
	MR2 (<=1% BCR-ABL ^{IS}) Rate (98.3% CI)[5]	XX	XX	XX

Time Point	COHORT A (45 MG) (N=xx)	COHORT B (30 MG) (N=xx)	COHORT C (15 MG) (N=xx)

Note: MR1 = Molecular response with 1-log reduction; MR2 = Molecular response with 2-log reduction; MR3 = Molecular response with 3-log reduction. BCR-ABLIS = BCR-ABL1 transcript level as measured by the International Scale. Patients are grouped by their planned treatment arm.

[1] The analysis includes safety population patients who have been on study for up to 12 months, including the following defined as failure: a) any patient with EOT/ET before 12 months, b) any patient with no molecular assessment performed or with no molecular assessment results at 12 months, and c) any patient with MR2 or better molecular assessment results (≤ 1% BCR-ABL1^{IS}) at baseline

[2] The Safety population include any patients who have received at least 1 dose of study drug

[3] EOT/ET = Discontinued treatment/early termination before 12 months.

[4] On Study but Not Achieved 12 month Time Point Since Randomized patients are excluded from denominator. All other categories are included in the denominator.

[5] The 2-sided type I error rate adjusted for the three statistical tests, using the Bonferroni method, is set at 0.05/3=0.0167. The 98.3% confidence interval is calculated using the binomial exact (Clopper-Pearson) method.

Table 25.2.1.5
Sensitivity Analysis 4 of Molecular Response Assessment by Treatment Arm[1]
Safety Population[2]

Time Point		COHORT A (45 MG) (N=xx)	COHORT B (30 MG) (N=xx)	COHORT C (15 MG) (N=xx)
Month 12	BCR-ABL^{IS} Ratio n (%)			
	n	XX	XX	XX
	> 10%	XX (XX.X)	XX (XX.X)	XX (XX.X)
	<=10% (MR1)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	<=1% (MR2)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	<=0.1% (MR3)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Early termination [3]	XX (XX.X)	XX (XX.X)	XX (XX.X)
	On Study but No BCR-ABL^{IS} Result	X (XX.X)	X (XX.X)	X (XX.X)
		X (XX.X)	X (XX.X)	X (XX.X)
	On Study but Not Achieved 12 month Time Point Since Randomized [4]			
		XX	XX	XX
	MR2 (<=1% BCR-ABL ^{IS}) Rate (98.3% CI)[5]			

Time Point	COHORT A (45 MG) (N=xx)	COHORT B (30 MG) (N=xx)	COHORT C (15 MG) (N=xx)

Note: MR1 = Molecular response with 1-log reduction; MR2 = Molecular response with 2-log reduction; MR3 = Molecular response with 3-log reduction. BCR-ABLIS = BCR-ABL1 transcript level as measured by the International Scale. Patients are grouped by their planned treatment arm.

[1] This sensitivity analysis includes safety population patients who have been on study for up to 12 months, including the following defined as failure: a) any patient with EOT/ET before 12 months, and b) any patient with no molecular assessment performed or with no molecular assessment results at 12 months. Patients with MR2 or better molecular assessment results (≤ 1% BCR-ABL1^{IS}) at baseline will be considered as failure or success based on the results at 12 months.

[2] The Safety population include any patients who have received at least 1 dose of study drug.

[3] EOT/ET = Discontinued treatment/early termination before 12 months.

[4] Patients who are on study but not achieved 12 month time point since randomized in the study are excluded from denominator. All other categories are included in the denominator.

[5] The 2-sided type I error rate adjusted for the three statistical tests, using the Bonferroni method, is set at 0.05/3=0.0167. The 98.3% confidence interval is calculated using the binomial exact (Clopper-Pearson) method.

Table 25.2.1.6
Sensitivity Analysis 5 of Molecular Response Assessment by Treatment Arm[1]
Safety Population[2]

Time Point		COHORT A (45 MG) (N=xx)	COHORT B (30 MG) (N=xx)	COHORT C (15 MG) (N=xx)
Month 12	BCR-ABL^{IS} Ratio n (%)			
	n	XX	XX	XX
	> 10%	XX (XX.X)	XX (XX.X)	XX (XX.X)
	<=10% (MR1)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	<=1% (MR2)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	<=0.1% (MR3)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Early Termination[3]	XX (XX.X)	XX (XX.X)	XX (XX.X)
	On Study but No BCR-ABL^{IS} Result	X (XX.X)	X (XX.X)	X (XX.X)
		X (XX.X)	X (XX.X)	X (XX.X)
	Baseline MR2 or Better[4]			
	On Study but Not Achieved 12 month Time Point Since Randomized [4]	XX	XX	XX
	MR2 (<=1% BCR-ABL ^{IS}) Rate (98.3% CI)[5]	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)

Time Point	COHORT A (45 MG) (N=xx)	COHORT B (30 MG) (N=xx)	COHORT C (15 MG) (N=xx)

Note: MR1 = Molecular response with 1-log reduction; MR2 = Molecular response with 2-log reduction; MR3 = Molecular response with 3-log reduction. BCR-ABLIS = BCR-ABL1 transcript level as measured by the International Scale. Patients are grouped by their planned treatment arm.

[1] This sensitivity analysis includes safety population patients who have been on study for up to 12 months, including the following defined as failure: a) any patient with EOT/ET before 12 months, and b) any patient with no molecular assessment performed or with no molecular assessment results at 12 months.

[2] The Safety population include any patients who have received at least 1 dose of study drug.

[3] EOT/ET = Discontinued treatment/early termination before 12 months.

[4] Patients who are on study but not achieved 12 month time point since randomized in the study or with MR2 or better molecular assessment results (≤ 1% BCR-ABL1^{IS}) at baseline are excluded from the analysis.

All other categories are included in the denominator.

[5] The 2-sided type I error rate adjusted for the three statistical tests, using the Bonferroni method, is set at 0.05/3=0.0167. The 98.3% confidence interval is calculated using the binomial exact (Clopper-Pearson) method.

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: **078,375**

SPONSOR: Takeda Development Center Americas, Inc.

95 Hayden Avenue

Lexington, MA 02421

USA

617-349-0200

Note: Takeda Development Center Americas, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as “sponsor,” or “Takeda.”

VERSION 4.0

DATE: 13 MAY 2025

Prepared by:

[redacted] PhD

[redacted], Oncology Statistics

REVISION/AMENDMENT HISTORY [redacted]

Amendment Version	Version Number	Date
Protocol Amd 4.0	1.0	06 June 2017
Protocol Amd 5.0	2.1	06 August 2019
Protocol Amd 5.0	2.2	16 December 2019
Protocol Amd 7.0	3.0	28 June 2024
Protocol Amd 7.0	3.1	28 November 2024
Protocol Amd 7.0	4.0	13 May 2025

Approval Signatures

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

Approvals:

[redacted]

13-May-2025 | 21:13:55 CEST

[redacted], PhD
[redacted],

Date

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
EQ	EuroQol
EWB	emotional well-being
FACT-G	Functional Assessment of Cancer Therapy - General
FACT-Leu	Functional Assessment of Cancer Therapy – Leukemia
FWB	functional well-being
HR-QoL	health-related quality of life

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
Ph+	Philadelphia chromosome positive
PK	pharmacokinetic(s)
PP	per-protocol
PWB	physical well-being
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
SWB	social well-being
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

1.0 INTRODUCTION

This Statistical Analysis Plan (SAP) 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 Protocol Version 7.0.

The SAP amendment V4.0 provides guidance for OPTIC final data analysis focusing on long term safety data for subjects who are still on treatment by OPTIC 5-year data-cut date. For efficacy endpoints, if analysis had been done and reported in the primary analysis CSR or 5-year CSR, then no repeated results are generated based on final data.

2.0 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) by 12 months and 24 months and rate of major cytogenetic response (MCyR) by 12 months
- To evaluate duration of MMR
- To characterize the rates of arterial occlusive events (AOEs), venous thromboembolic events (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

- Correlation of tumor cell and plasma biomarkers with ponatinib efficacy and safety.
- Quality of Life (QoL) and health outcomes.

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

- Correlation of tumor cell and plasma biomarkers with ponatinib efficacy and safety
- QoL and health outcomes as measured by EQ-5D-5L and FACT-Leu

3.0 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 16.5.1.1 of 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 15 mg 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 intent-to-treat (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).

4.0 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 (ie, 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. For this final CSR, ITT Population will include patients who were still on study treatment or under study follow-up after 5-year CSR data cut date (15MAY2024) only.

Safety Population: The safety 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. For this final CSR, Safety Population will include patients who were still on study treatment or under study follow-up after 5-year CSR data cut date (15MAY2024) only.

Per-protocol (PP) 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 [eg, starting dose that was not the one to which the patient was randomized], no post-baseline BCR-ABL^{IS} assessment). For this final CSR, Per-protocol Population will include patients who were still on study treatment or under study follow-up after 5-year CSR data cut date (15MAY2024) only.

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 based on all randomized population who were still on study treatment or under study follow-up after 5-year CSR data cut date (15MAY2024):

- Numbers of patients in ITT, Safety, and PP populations
- Numbers of patients still on study treatment
- Numbers of patients discontinued from treatment
- Primary reason for treatment discontinuation

The following data for survival follow-up will be listed based on safety population:

- Follow-up status
- Duration of follow-up
- Date of Death
- Cause of Death

4.4 Major Protocol Deviations

Major protocol deviations that occurred after 5-year CSR data-cut will be identified prior to database lock and will be listed and summarized.

4.5 Concomitant Medications

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) taken after 5-year CSR will be summarized. Medications belonging to categories of interest such as aspirin and anticoagulants will be identified and summarized.

4.6 Efficacy Analyses

4.6.1 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
- QoL and health outcomes as measured by EQ-5D-5L and FACT-Leu

4.6.2 Definitions of Efficacy Endpoints

The primary and secondary efficacy endpoints are listed in Section 2.2. This section provides the definitions of the endpoints are included in the final CSR.

4.6.2.1 Event-Related Definitions

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

Progression to AP is defined as:

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

or

- ≥ 20% basophils in peripheral blood or bone marrow

or

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

or

- < 100×10^9 platelets/L in peripheral blood unrelated to therapy

or

- Cytogenetic, genetic evidence of clonal evolution

and

- No extramedullary disease

Progression to BP is defined as:

- ≥ 30% blasts in peripheral blood or bone marrow

or

- Extramedullary disease other than hepatosplenomegaly

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

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

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.

4.6.3 Primary Endpoint Analysis

The primary analysis of the primary endpoint for each cohort had been completed in previous Primary Endpoint (PA) CSR and is not repeated in this final CSR.

4.6.4 Secondary Efficacy Endpoint Analyses

4.6.4.1 Secondary Efficacy Endpoints

The analyses of secondary molecular efficacy endpoints had been completed in previous PA CSR and 5-year CSR and are not repeated in this final CSR. OS and PFS for ITT Population who were still on study treatment after 5-year CSR only are listed only. .

4.7 Safety Analysis

All patients receiving at least 1 dose of study drug will be considered evaluable for safety. Safety analyses are performed based on the safety 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. For this final CSR, only AEs occurred after 5-year CSR data-cut date will be displayed. Rates of AEs and SAEs will be summarized for treatment-emergent events (TEAEs), and all AEs will be listed.

4.7.1 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 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

Both Venous thrombotic events (VTE) and AOEs will be listed.

4.7.2 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

4.7.3 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.

4.7.4 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. Study drug tolerability is summarized for safety population and for the period after 5-year CSR data-cut date only.

4.7.5 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. Study drug exposure is summarized for safety populations only.

4.7.6 Laboratory Tests

Listings of laboratory test results are generated.

4.7.7 Blood Pressures

Blood pressure results are listed.

4.7.8 ECG and ECHO

ECG and ECHO results are listed.

4.8 Changes in the Statistical Analysis Plan

Reference materials for this statistical analysis plan include Clinical Study Protocol AP24534-14-203 Amendment 7 (Protocol Amendment dated 07 April 2021). This SAP amendment version 4.0 provides OPTIC final data analysis focusing on long term safety and survival follow-up data for subjects who are still on treatment by OPTIC 5-year data-cut. For efficacy endpoints, if analysis had been done and reported in the primary analysis CSR or 5-year CSR, then no repeat results will be generated based on final data.

5.0 REFERENCES

O'Brien, S. G., Guilhot, F., Larson, R. A., Gathmann, I., Baccarani, M., Cervantes, F., et al. 2003. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med,* 348(11), 994-1004.

Ulm, K. 1990. A simple method to calculate the confidence interval of a standardized mortality ratio (SMR). *Am J Epidemiol,* 131(2), 373-5.

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, Takeda - DocuSign GxP (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact Takeda - DocuSign GxP:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: DocuSigneSignaturePlatform@mytakeda.com

To advise Takeda - DocuSign GxP of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at DocuSigneSignaturePlatform@mytakeda.com and in the body of such request you must state: your previous email address, your new email address. Contact the global service desk to request a name change in DocuSign

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from Takeda - DocuSign GxP

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to DocuSigneSignaturePlatform@mytakeda.com and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with Takeda - DocuSign GxP

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to DocuSigneSignaturePlatform@mytakeda.com and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify Takeda - DocuSign GxP as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by Takeda - DocuSign GxP during the course of your relationship with Takeda - DocuSign GxP.