Title: A Phase 2/3 Open-label Study to Evaluate Safety and Efficacy of Ponatinib, Followed by a Randomized Study of Ponatinib Versus Nilotinib in Patients with Chronic Myeloid Leukemia in Chronic Phase (CP-CML) Resistant to Imatinib

NCT Number: NCT02627677

SAP Approve Date: 31 July 2016

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STATISTICAL ANALYSIS PLAN (SAP)

FOR

AP24534-15-303

PROTOCOL TITLE: A Randomized, Open-Label Study of Ponatinib Versus Nilotinib in Patients with Chronic Myeloid Leukemia in Chronic Phase Following Resistance to Imatinib

PROTOCOL NUMBER: AP24534-15-303

IDENTIFIER: ClinicalTrials.gov: NCT02627677

EudraCT Number: 2015-001318-92

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ORIGINAL ISSUE DATE: Version 1.0 **31 July** 2016

REVISION/AMENDMENT HISTORY:

Protocol Version	SAP Version	SAP Date
Original Protocol Version 1.0		
Protocol Version 2.0	Original SAP Version 1.0	31 July 2016
Protocol Version 2.0	SAP Version 2.0	23 July 2020

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE(s)	adverse event(s)
AESI(s)	adverse event(s) of special interest
AOE(s)	arterial occlusive event(s)
AP	accelerated phase
ARIAD	ARIAD Pharmaceuticals, Inc.
AUC	area under the curve
BCR-ABL	Breakpoint Cluster Region-Abelson
$BCR\text{-}ABL^{IS}$	BCR-ABL 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(s)	confidence interval(s)
CM(s)	concomitant medication(s)
CMH	Cochran Mantel-Haenszel
CML	chronic myelogenous leukemia/chronic myeloid leukemia
C_{max}	maximum plasma concentration
CP	chronic phase
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
EAIR	exposure-adjusted incidence rate
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FACT-Leu	Functional Assessment of Cancer Therapy – Leukemia
FAS	Full Analysis Set
HR-QoL	health-related quality of life
IS	international scale
ITT	Intent-to-Treat
LVEF	left ventricular ejection fraction
MCyR	major cytogenetic response
MedDRA	Medical Dictionary for Regulatory Activities
MMR	major molecular response
MR1	molecular response with 1-log reduction
MR2	molecular response with 2-log reduction
MR3/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

Abbreviation	Term
PCR	polymerase chain reaction
PCyR	partial cytogenetic response
PFS	progression-free survival
Ph+	Philadelphia chromosome positive
PK	pharmacokinetic(s)
PP	Per-Protocol
PRO	patient-reported outcome
QD	once daily
QoL	quality of life
QTcF	QT interval corrected (Fridericia)
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SD	standard deviation
SMQ	Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query
TEAE(s)	treatment-emergent adverse event(s)
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
VAS	visual analog scale
VOE(s)	vascular occlusive event(s)
VTE(s)	venous thromboembolic event(s)
WHO	World Health Organization

1 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 analysis for the primary endpoint and the analyses for secondary endpoints, based on the Protocol Version 2.0.

The study accrual is terminated prematurely based on the consideration of landscape change in availability of 2nd line nilotinib treated patients. At the time of accrual termination, a total of 44 patients have been enrolled into the study and randomized to receive the study drugs. Based on this change in situation, the efficacy analyses will no longer be sufficiently powered per the study design. Therefore, efficacy data will be summarized descriptively, and no formal statistical tests will be conducted as originally planned in the protocol.

Instead of a full clinical study report (CSR), an abbreviated CSR will be submitted, as decided by the study team. Since an abbreviated CSR will include all safety information as included in a full report, whereas efficacy information will be concise and not as comprehensive as in a full CSR, the analysis will be planned accordingly in this document.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

- To demonstrate the efficacy of ponatinib administered at 2 starting doses (30 and 15 mg QD) compared to nilotinib administered at 400 mg BID in patients with chronic phase chronic myeloid leukemia (CP-CML) who are resistant to imatinib, as measured by major molecular response (MMR) by 12 months.

2.1.2 Key Secondary Objectives

- To characterize, according to each arm and ponatinib starting dose, the rates of vascular occlusive events (VOEs), adverse events (AEs), and serious adverse events (SAEs).
- To characterize, according to each arm and ponatinib starting dose, the rate of cytogenetic responses and molecular responses other than MMR.
- To further characterize efficacy according to each arm and ponatinib starting dose, including time to response, duration of cytogenetic and molecular response, duration of therapy, progression free survival (PFS), overall survival (OS), and impact of dose escalation after loss of response (ponatinib cohorts only).

2.1.3 Other Secondary Objectives

- To characterize, according to each arm and ponatinib starting dose, the rate of discontinuation, dose reductions, and interruptions.
- To characterize, according to each arm and ponatinib starting dose, the rate of hematologic responses.

2.1.4 Exploratory Objectives

CCI [redacted]

2.2 Study Endpoints

2.2.1 Primary Endpoint

- MMR by 12 months for each cohort

2.2.2 Key Secondary Endpoints

- Cytogenetic response rates:
  a. Major cytogenetic response (MCyR) by 12 months
  b. Complete cytogenetic response (CCyR) by 12 months
- Molecular response rates: MR2 (≤1% BCR-ABL^{IS}), MR3/MMR (≤0.1% BCR-ABL^{IS}), MR4 (≤0.01% BCR-ABL^{IS}), MR4.5 (≤0.0032% BCR-ABL^{IS}) at 3-month intervals until end-of-treatment and MR1 (≤10% BCR-ABL^{IS}) at 3 months
- Safety
  a. Rate of arterial occlusive events (AOEs) and VOEs in each cohort
  b. Rate of AEs in each cohort
  c. Rate of SAEs in each cohort
- Time to response
- Duration of response:
  a. MR2 and MMR at 3, 6, 9, and 12 months, and then at 3-month intervals until completion of treatment
  b. MCyR at 12 and 24 months, by cytogenetic analysis
  c. Duration of response in responders
  d. Duration of therapy
- PFS
- OS

2.2.3 Other Secondary Endpoints

- Hematologic response rates: complete hematologic response (CHR)

- Tolerability:
  a. Rate of discontinuation due to AEs in each cohort
  b. Rate of dose reductions due to toxicity (prior to response) in each cohort
  c. Rate of dose interruptions in each cohort
- Rate of progression to accelerated phase (AP) or blast phase (BP) CML

2.2.4 Exploratory Endpoints

CCI [redacted]

3 STUDY DESIGN

3.1 Study Design

This is a multi-center, randomized study to demonstrate the efficacy and safety of two starting doses of ponatinib as compared to nilotinib. Eligible patients must have CP-CML, be resistant to first-line imatinib treatment and not received any other tyrosine kinase inhibitor (TKI) therapy.

Patients will be randomized to receive once daily oral administration of either 30 mg ponatinib QD (Cohort A), or 15 mg ponatinib QD (Cohort B), or 400 mg nilotinib BID (Cohort C). They will be randomized in a ratio of 1:2:1, respectively. The primary endpoint of MMR by 12 months is defined according to standard criteria as ≤0.1% BCR-ABL/ABL^{IS}. Upon achievement of MMR, patients in Cohort A will have their daily dose of ponatinib reduced to 15 mg and patients in Cohort B will have their daily dose of ponatinib reduced to 10 mg. The dose of nilotinib for patients in Cohort C will not be adjusted based on response.

Treatment will continue until lack of response at 12 months is established, intolerance develops or response is lost. In the ponatinib arms, Cohorts A and B, patients who achieve and then lose response after dose reduction for MMR may have their dose escalated to their initial dose and remain on study. In the nilotinib arm, Cohort C, patients who lose response will discontinue study treatment.

The study will assess hematologic response, cytogenetic response, and molecular response, as well as additional measures of efficacy including time to responses, and duration of responses by starting dose and after dose reduction. PFS and OS data will also be collected and analyzed.

Adverse event (AE) rates and the rates of VOEs, in particular, will be measured. Assessments will be according to standard international criteria. The duration of patient participation will be 60 months for all patients, unless they withdraw prior to that based on the withdrawal criteria defined within the protocol.

3.1.1 Schedule of Events

Table 3 in the protocol lists the screening and study procedures to be done through Cycle 12. Table 4 in the protocol lists the procedures to be done after Cycle 12 through the end of the study. Unless otherwise specified, the timing in which Cycle 1 tests are performed should be repeated in later cycles.

Cycle visit samples or activities should occur within 3 days of the scheduled study day unless otherwise noted in the Schedule of Events (Section 12.1 of the protocol).

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 1:2:1 ratio to receive either ponatinib in one of two starting doses or nilotinib:

- Cohort A: 30 mg ponatinib QD with reduction to 15 mg at 3, 6, 9, or 12 months upon achievement of MMR.
- Cohort B: 15 mg ponatinib QD with reduction to 10 mg at 3, 6, 9, or 12 months upon achievement of MMR.
- Cohort C: 400 mg nilotinib BID.

A cycle of therapy will comprise 28 days of treatment, regardless of dose.

The randomization will be stratified based on the patient's baseline age (≥60 vs <60 years) and best response to prior imatinib therapy (CCyR or MR2 or better, yes/no). Randomization procedures should be performed following confirmation of eligibility and prior to the initiation of assigned treatment.

3.4 Study Treatment

The starting dose of study drug will be 30 mg ponatinib QD (Cohort A), 15 mg ponatinib QD (Cohort B), or 400 mg nilotinib BID (Cohort C), taken orally. Study drug will be self-administered by the patient on a daily schedule. Patients in Cohort A will have their daily dose of ponatinib reduced to 15 mg and patients in Cohort B will have their daily dose of ponatinib reduced to 10 mg if MMR has been achieved.

Study treatment will be administered only to eligible randomized patients at qualified centers.

3.4.1 Ponatinib Treatment for Patients in Cohorts A and B

The starting dose of study drug will be 30 mg ponatinib QD (Cohort A), 15 mg ponatinib QD (Cohort B). Each 28-day dosing period is referred to as 1 cycle. Patients will be assessed for MMR and MCyR as described below, and doses will be modified according to response. Doses may also be modified to manage AEs.

3.4.1.1 Mandatory Dose Reduction for Response Scheme in Ponatinib Cohorts A and B

Patients will be assessed for molecular and cytogenetic response at 3-month intervals. Patients in the ponatinib cohorts will have their doses reduced upon attainment of MMR or MCyR, as defined in Sections 4.7.2.1 and 4.7.2.2. No dose reduction for response will be implemented for patients in the nilotinib cohort. The dose reduction scheme is described in the Table below.

Response Criteria	Time Point	Value	Cohort	Action
MMR (≤0.1%)	3 months and every subsequent 3 months	MMR	A	Reduce dose to 15 mg
			B	Reduce dose to 10 mg
			C	No change in dose
MCyR by BM cytogenetics	12 months	MCyR	A	Reduce dose to 15 mg
			B	Reduce dose to 10 mg
			C	No change in dose
		Not in MCyR	A, B or C	Discontinue from study

MMR is defined as a ≤0.1% ratio of BCR-ABL to ABL transcripts on the IS (BCR-ABL^{IS}), measured by real-time quantitative polymerase chain reaction (PCR).

MCyR is defined according to standard criteria as ≤35% Ph+-containing metaphases (typically <7/20 involved metaphases), that is, as either a PCyR or a CCyR. Increasingly, patient monitoring is being performed by quantitation of BCR-ABL transcript from a standard according to the international scale (IS). Using such monitoring, ≤1% BCR-ABL/ABL^{IS} (also denoted as MR2) is taken to be equivalent to CCyR.

Patients will undergo a baseline BM aspirate and cytogenetics to establish the diagnosis and eligibility. They will then undergo molecular monitoring at 3-month intervals for the assessment of response. In the ponatinib arms (Cohorts A and B), the assessment will also inform the decision regarding dose reduction. They will undergo a BM aspirate with cytogenetics after 12 cycles, which will be used to assess cytogenetic response at 12 months and to inform the decision regarding dose reduction, at end of treatment as specified in the Schedule of Events (Table 4 in the protocol), and other time points depending on response.

Note: patients may undergo dose reduction for adverse events prior to the achievement of MMR. This should not affect the assessment of response and the mandated dose reduction in patients enrolled in the ponatinib cohorts upon its attainment.

The schedule of patient assessment for mandatory response-related dose reduction in Cohorts A and B is as follows:

At 3 months, patients in Cohorts A and B will have their dose reduced to 15 mg and 10 mg, respectively, if they are in MMR. If not, they will continue at their current dose until the 6-month assessment.

At 6 months, patients in Cohorts A and B will have their dose reduced to 15 mg and 10 mg, respectively if they are in MMR. If not, they will continue at their current dose until the 9-month assessment.

At 9 months, patients in Cohorts A and B will have their dose reduced to 15 mg and 10 mg, respectively, if they are in MMR. If not, they will continue at their current dose until the 12-month assessment.

At 12 months, all patients will undergo a BM aspirate and cytogenetics. Patients in Cohorts A and B will have their dose reduced to 15 mg and 10 mg, respectively, if they are in MMR or in MCyR, and will continue therapy. If not in MCyR, they will discontinue therapy.

3.4.1.2 Loss of Response after Dose Reduction for MMR or MCyR in Cohorts A and B

Patients being treated with ponatinib who achieve MMR at any time point, undergo dose reduction, and then lose MMR, as determined by real-time quantitative PCR assessment (Section 4.7.2.1), are candidates for dose re-escalation to their starting dose, in the absence of AEs requiring dose modification. Patients who achieve MCyR, but not MMR, at 12 months also will undergo dose reduction. These patients who subsequently lose MCyR are also candidates for dose escalation at the discretion of the physician.

Patients will be monitored with a cytogenetic assessment at 12 months and molecular response assessments every 3 months according to the Schedule of Events (Table 3 and Table 4 in the protocol). Any patient who has a greater than 1-log increase in transcript level should also have a BM cytogenetic assessment performed unless the patient remains in MR2. If the cytogenetic assessment indicates loss of MCyR, dose escalation may be considered. If the cytogenetic assessment does not demonstrate loss of MCyR, continued monitoring is indicated.

Patients may be dose re-escalated as follows:

Patients may only undergo dose re-escalation if they do not have ongoing AEs necessitating treatment at 10 mg or 15 mg as per Section 14.4.2 of the protocol (Dose Modifications for Adverse Drug Reactions).

For patients in Cohort A, re-escalate to the starting dose of 30 mg. For patients in Cohort B, escalate to the starting dose of 15 mg.

If patients regain MCyR after dose escalation, continue their therapy at the escalated dose and monitor according to the Schedule of Events.

If patients do not regain MCyR after 6 months of therapy at the escalated dose, they must be discontinued from the study.

The dose re-escalation scheme is described in the table below.

Current Response Criteria	Time Point	Cohort	Action
Loss of MCyR by cytogenetics	12 months or later	A	Re-escalate to 30 mg[a]
		B	Re-escalate to 15 mg[a]
If • Loss of MR2 (ie, ≥1% BCR-ABL) and >10-fold ↑in BCR-ABL from nadir **or** • BCR-ABL >10%	Any time after achievement of MCyR or MMR	A	Perform BM cytogenetics; if loss of MCyR then re-escalate to 30mg[a]; if no loss of MCyR, continue to monitor according to SOE
		B	Perform BM cytogenetics; if loss of MCyR then re-escalate to 15 mg[a]; if no loss of MCyR, continue to monitor according to SOE

[a] unless dose-reduction was due to AEs

3.4.2 Nilotinib Treatment for Patients in Cohort C

The starting dose of study drug will be 400 mg nilotinib BID (Cohort C). Each 28-day dosing period is referred to as 1 cycle. Patients will be assessed for MMR and MCyR as described above, but in contrast

to the ponatinib arms, doses will not be modified according to achievement of response. Doses may be modified to manage AEs.

3.5 Determination of Sample Size

The primary endpoint for this study will be MMR rate by 12 months. The primary analysis of the primary endpoint of MMR will be performed using a 2-sided alpha = 0.024 for each comparison.

A sample size of 150 patients in each Cohort A and C (ponatinib 30 mg and nilotinib, respectively) will distinguish a favorable MMR rate of 45% for ponatinib from a null or an uninteresting MMR rate of 25% for nilotinib with a nominal 90% power to detect an improvement in MMR of 20%.

The sample size of 300 patients in Cohort B and 150 patients in Cohort C will distinguish a favorable MMR rate of 40% for ponatinib from a null or an uninteresting MMR rate of 25% for nilotinib with approximately 80% power to detect an improvement in MMR of 15%.

Per the original study design, the overall total sample size will be 600 patients with 150 patients in the ponatinib 30 mg starting dose cohort (Cohort A), 300 patients in the ponatinib 15 mg starting dose cohort (Cohort B), and 150 patients in the nilotinib cohort (Cohort C).

The study accrual is terminated prematurely based on the consideration of landscape change in availability of 2nd line nilotinib treated patients. At the time of accrual termination, a total of 44 patients have been enrolled into the study and randomized to receive the study drugs.

4 STATISTICAL ANALYSES AND METHODS

4.1 General Considerations

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

Eligible CP-CML patients will be randomized to one of 3 cohorts (Cohort A: 30 mg ponatinib QD, Cohort B: 15 mg ponatinib QD, Cohort C: 400 mg nilotinib BID) in a 1:2:1 fashion. Upon achievement of MMR, patients assigned to ponatinib 30 mg will have their daily dose of ponatinib reduced to 15 mg, and patients assigned to ponatinib 15 mg will have their daily dose of ponatinib reduced to 10 mg. Patients will be stratified by age at baseline (≥60 years versus <60 years) and best response to prior imatinib therapy (CCyR or MR2 or better yes/no).

Categorical data will be summarized by the number and percentage of patients in each category. Continuous variables will be summarized by descriptive statistics (ie, n, mean, standard deviation [SD], median, minimum, and maximum). Two-sided confidence interval (CI) will be provided where appropriate.

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 concomitant medication (CM) will be imputed using a conservative approach. The imputation methods are available upon request.

Due to earlier termination of study accrual, no statistical inference will be made, and no formal statistical tests will be conducted as originally planned in the protocol. The final analysis is planned to be performed for abbreviated CSR.

4.2 Analysis Populations

Intention-to-Treat (ITT) Population: The ITT population includes all patients who are randomized to the study. Patients will be analyzed according to the treatment to which they were assigned. Patients who are subsequently determined to be assigned to an incorrect stratum will be analyzed according to the stratum to which they were assigned at randomization.

Full Analysis Set (FAS): The FAS includes all patients in the ITT population as defined above who have b2a2/b3a2 BCR-ABL transcript types at study entry (patients for whom a BCR-ABL^{IS} ratio can be determined).

Safety Population: The safety population for each cohort includes all patients who have received at least 1 dose of study drug. The primary analyses of safety will be based on the safety population where data will be analyzed according to the treatment to which patient is actually assigned.

Per-Protocol (PP) Population: The PP 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, and administration of incorrect dose (eg, dose that was not the one to which the patient was randomized). Major protocol violations will be finalized and documented prior to database lock. The PP analyses may only be performed 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 in ITT population, FAS, safety population, and PP population
- 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-leukemia 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, height, body mass index (BMI), and ECOG score

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

4.6 Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (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

Due to earlier termination of study accrual, the efficacy analyses (including primary analysis for primary endpoint, MMR rate by 12 months) will no longer be sufficiently powered per the original study design. Therefore, efficacy data will be summarized descriptively, and no formal statistical tests will be conducted as originally planned in the protocol.

4.7.1 Efficacy Assessments

Efficacy assessments comprise at least:

- BCR-ABL transcript assessment to determine molecular response
- Bone marrow aspirates for assessment of cytogenetic response
- Complete blood count for assessment of hematologic response
- PFS and Survival follow-up

4.7.2 Definitions of Efficacy Endpoints

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

4.7.2.1 Molecular Response Definitions

Major molecular response (MMR) is defined as a ≤0.1% ratio of BCR-ABL to ABL transcripts on the international scale (BCR-ABL^{IS}), measured by real-time quantitative PCR.

MR1 at 3 months is the proportion of patients achieving a ratio of ≤10% BCR-ABL to ABL transcripts on the international scale at 3 months.

Molecular response: MR2, MR4, and MR4.5 are defined as ≤1%, ≤ 0.01%, and ≤ 0.0032% BCR-ABL^{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.

Time to MMR is defined as the interval between the randomization date and the first date at which the criteria for MMR are met.

Duration of MR2/MMR/MR4/MR4.5 is defined as the interval between the first assessment at which the criteria for MR2/MMR/MR4/MR4.5 are met until the earliest date at which loss of MR2/MMR/MR4/MR4.5 occurs (see below), or the criteria for progression (see Section 4.7.2.4) are met. Patients remaining in MR2/MMR/MR4/MR4.5 will be censored at the last date at which the criteria for MR2/MMR/MR4/MR4.5 are met.

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 progression to AP- or BP-CML, or death due to CML.

Loss of MR2 is defined as an increase to >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 progression to AP- or BP-CML, 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 progression to AP- or BP-CML, 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 progression to AP- or BP-CML, or death due to CML.

4.7.2.2 Cytogenetic Response Definitions

Rate of major cytogenetic response (MCyR) by 12 months is the proportion of patients achieving CCyR or PCyR at any time within 12 months after randomization.

Cytogenetic response is the percentage of Ph+ metaphases in bone marrow (peripheral blood may not be used), with a review of a minimum of 20 metaphases. Responses are defined as follows:

Major cytogenetic response (MCyR): CCyR or PCyR

- Complete cytogenetic response (CCyR): 0% Ph+ metaphases
- Partial cytogenetic response (PCyR): >0% to 35% Ph+ metaphases

Rate of complete cytogenetic response (CCyR) by 12 months is the proportion of patients achieving CCyR at any time within 12 months after randomization. Additionally, CCyR at 12 months will be calculated using only cytogenetic criteria. Additional analyses may be performed that will consider patients who achieve MR2 to have achieved CCyR.

Time to MCyR is defined as the interval from randomization until the criteria for MCyR are first met.

Duration of MCyR is defined as the interval between the first assessment at which the criteria for MCyR are met until the earliest date at which loss of MCyR occurs, or the criteria for progression (Section 4.7.2.4) are met. Patients remaining in response will be censored at their latest assessment (either cytogenetic or molecular).

Loss of MCyR is defined as a single BM assessment with Ph+ metaphases >35% after achievement of MCyR (CCyR or PCyR or MR2).

Loss of CCyR is defined as an increase in the Ph+ metaphases in BM to >0% in a single BM assessment.

Loss of PCyR is defined as an increase in the Ph+ metaphases in BM from >0% to 35% to >35% in a single BM assessment.

4.7.2.3 Hematologic Response Definitions

Complete hematologic response (CHR) rate is defined as the proportion of patients achieving CHR at any time after initiation of study treatment. CHR will be confirmed no earlier than 28 days later.

CHR is defined as achieving all of the following measurements:

- White blood cells (WBC) ≤ institutional upper limit of normal (ULN)
- Platelets <450 x 10^9/L
- 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 x 10^9/L
- Platelet count that rises to ≥600 x 10^9/L
- Progressing splenomegaly 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

Progression-free survival (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 AP- or BP-CML), or death due to any cause, censored at the last response assessment.

Progression to AP-CML 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-CML is defined as:

- ≥ 30% blasts in peripheral blood or bone marrow

  or

- Extramedullary disease other than hepatosplenomegaly

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

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

Overall Survival (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 to be alive.

4.7.2.5 Time Windows for Analyses of Molecular and Cytogenetic Response

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

Planned Assessment[2]	**Time window**
Baseline	As specified in 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 2 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

Per the original plan in the protocol, the primary analysis of the primary endpoint (ie, MMR rate by 12 months) will be performed using a stratified Cochran Mantel-Haenszel (CMH) test. The study will be stratified by age at baseline (≥60 versus <60 years) and best response to prior imatinib therapy (CCyR or MR2 or better, yes/no) to compare the MMR rate by 12 months between patients receiving either dose level of ponatinib (initial dose: 30 mg once daily [QD] or 15 mg once daily [QD]) and patients receiving nilotinib (initial dose: 400 mg BID) and will follow a testing procedure to ensure an overall 2-sided Type I error rate of <0.05 (see Section 16.11 of the protocol).

As a result of earlier termination of study accrual, the primary analysis of the primary endpoint (ie, MMR rate by 12 months) will only be performed descriptively with point estimate and its 95% CI by each cohort for MMR rate by 12 months, and no formal statistical tests (eg, CMH test) will be conducted as originally planned in the protocol.

The primary analysis will be based on the Full Analysis Set (all patients randomized to a treatment group for whom a BCR-ABL^{IS} ratio can be determined at baseline). A sensitivity analysis of the primary endpoint will be performed on the ITT population, with patients not evaluable treated as non-responders.

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

The following patients will be analyzed as responders in the primary analysis:

- Patients who meet the criteria for MMR by 12 months after randomization

All other patients will be analyzed as non-responders in the primary analysis, including randomized patients without follow-up (and any patients who meet the criteria for MMR at study entry).

4.7.4 Secondary Efficacy Endpoint Analyses

As a result of earlier termination of study accrual, the secondary efficacy endpoint analyses will only be performed descriptively with point estimates and 95% confidence intervals (CIs) by each cohort, and no formal statistical tests (eg, CMH test) will be conducted as originally planned in the protocol.

4.7.4.1 Key Secondary Efficacy Endpoints

Descriptive statistics summary with point estimates and 95% CIs will be performed on the following molecular key secondary endpoints (MR3/MMR at 24 months; MR4 at 24 months; MR4.5 at 24 months, MR1 at 3 months) and key secondary cytogenetic endpoints (CCyR at 12 months; MCyR by 12 months), by each cohort.

Analyses of molecular key secondary endpoints will be performed on the Full Analysis Set. Analyses of cytogenetic key secondary endpoints will be performed on the ITT population.

Note that at some analysis time points not all key secondary endpoints will be mature (eg, molecular key secondary endpoints will not be mature at interim analysis or 12-month analysis – see Section 4.7.4.3 for the statistical handling of these key secondary endpoints).

The additional key secondary efficacy endpoints to be descriptively summarized in the same fashion are listed below.

- Molecular response rates: MR2, MR3/MMR, at 3-month intervals, and MR4, MR4.5 at 3-month intervals other than 24 months
- CCyR by 12 months
- Time to response
- Duration of response:
    1. MR2 and MMR at 12, 18, and 24 months
    2. MCyR at 12 and 24 months
    3. Duration of response in responders
    4. Duration of therapy
- PFS
- OS

PFS and OS will be estimated using the Kaplan-Meier method, the median time to event and its 95% CI will be provided. Descriptive statistics (eg, mean, median, minimum and maximum, etc.) will be provided for time to response, duration of response in responders and duration of therapy.

4.7.4.2 Analysis Methods for Other Secondary Efficacy Endpoints

The analysis of other secondary efficacy endpoints of molecular response rates, cytogenetic response rates, CHR rate and rate of progression to AP- or BP-CML will be performed descriptively with point estimates and 95% CIs by each cohort.

Analyses of molecular response rates will be performed on the Full Analysis Set. All other analyses will be performed on the ITT population.

4.7.4.3 Data Handling Rules for Secondary Efficacy Endpoint Analyses

For the secondary endpoints of cytogenetic responses, at any given cytogenetic assessment after baseline, if fewer than 20 metaphases are examined, the rules in Table 3 will apply to the determination of MCyR:

Table 3 Determination of MCyR by Cytogenic Assessment

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

Ph+ = Philadelphia chromosome positive; PCyR = partial cytogenetic response

Determination of CCyR by cytogenetic assessment will require at least 20 metaphases examined. For the analyses of secondary endpoints of MCyR, CCyR, MR2, MR4.5, MR4, and CHR, if patients do not have a baseline assessment or post-baseline response assessment, the patients will be considered as non-responders. Patients who meet the criteria for response at baseline will also be analyzed as non-responders.

4.7.4.4 Subgroup Analyses of the Primary Endpoint and Secondary Efficacy Endpoints

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

- Age (<60, ≥60 years)
- Gender
- Race
- Geographic region
- T315I mutation history (Yes, No)
- Best response to prior imatinib therapy (CCyR, MR2 or better)
- Other disease-related prognostic factors

As a result of earlier termination of study accrual, the subgroup analyses for the primary endpoint and secondary efficacy endpoints may not be performed when not warranted based on numbers of patients in subgroups.

4.8 Safety Analysis

Safety analyses will be 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. AEs and SAEs will be summarized for treatment-emergent adverse events (TEAEs) and all AEs will be listed.

4.8.1 Analysis of Vascular Occlusive Events

Number and percentages of patients who develop VOEs will be summarized for each cohort. VOEs will be categorized as follows:

- Arterial occlusive events (AOEs)
    - Cardiovascular occlusive events
    - Cerebrovascular occlusive events
    - Peripheral vascular occlusive events
- Venous thromboembolic events (VTEs)

Details for classification of specific events as VOEs are given in Section 14.4.1.1 of the protocol.

The primary analysis of AOEs and VTEs will be an exposure-adjusted incidence rate, as follow-up may differ among the cohorts. The exposure-adjusted incidence rate is calculated as number of patients with the AE divided by total treatment exposure time.

The following additional descriptive analyses will be performed to characterize VOEs:

- Time to onset: calculated as date of first VOE – first dose date + 1
- Dose at onset: dose of ponatinib or nilotinib taken immediately prior to onset of first VOE.

Baseline risk factors for the occurrence of VOEs will be evaluated for all patients, and will include:

- History of arterial occlusive disease
- History of other cardiovascular disease
- History of venous thromboembolism
- Hypertension
- History of diabetes/hyperglycemia
- History of smoking
- Obesity
- History of hyperlipidemia
- Age
- Gender
- Other risk factors

4.8.2 Analysis of Categories of Adverse Events

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-related AEs and SAEs, crude rates as well as the frequency of occurrence by overall toxicity, categorized by toxicity grades (severity) will be summarized for each cohort.

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

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 Section 14.2.1 of the protocol.
- Dose interruptions in each dose cohort. Dose interruption is defined as at least 3 consecutive days gap with no dose taken due to AEs.

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

Time to first dose interruption due to AEs and time to first dose reduction due to AE will also be summarized to characterize length of dose interruptions and reductions.

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

The absolute change from baseline will be summarized at each of the laboratory timepoints, using descriptive statistics (ie, n, mean, SD, median, minimum and maximum) for each cohort.

Shifts in laboratory parameters from baseline to the best post-baseline value (ie, minimum severity grade) and worst post-baseline value (ie, maximum severity grade) in term of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be summarized up to 30 days after the last dose date.

Listings of laboratory test results will be generated.

4.8.7 Vital Signs and Blood Pressures

The actual values of vital sign parameters (ie, systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, temperature, height, and weight) will be summarized at all planned timepoints for each cohort using descriptive statistics (ie, n, mean, SD, median, minimum and maximum). Change of vital signs from baseline values will also be summarized at all planned timepoints.

Shift from baseline in blood pressure over time will be summarized.

Vital sign values will also be presented in a by-patient listing.

4.8.8 12-Lead Electrocardiogram (ECG)

The absolute values and absolute change from baseline of electrocardiogram (ECG) parameters including heart ventricular rate, QT duration, and QT interval corrected (Fridericia) (QTcF) interval will be summarized at each timepoint using descriptive statistics (ie, n, mean, SD, median, minimum and maximum). Maximum QTcF changes from baseline will also be summarized similarly.

In addition, a categorical analysis of QTcF intervals will be performed for each time point. The number and percentage of patients in each QTcF interval (eg, < 450 msec, ≥ 450 - < 480 msec, ≥ 480 - < 500 msec, and ≥ 500 msec) will be summarized at each time point. Categories of changes from baseline (eg, ≥ 30 - < 60 msec and ≥ 60 msec) will be summarized as well.

4.8.9 Echocardiogram (ECHO)

Left ventricular ejection fraction (LVEF) at baseline and LVEF shift from baseline to the minimum post-baseline value will be summarized up to 30 days after the last dose date.

4.8.10 ECOG Performance Status

ECOG performance status over time will be summarized by each cohort.

4.9 Exposure-Response Analysis

No exposure-response analysis will be performed due to earlier termination of study accrual.

4.10 Quality of Life / Health Outcomes Analysis

QoL and health outcomes measures are being collected using the EQ-5D-5L and FACT-Leu instruments. Patient-reported outcome (PRO) assessments using the EQ-5D-5L and FACT-Leu will be

analyzed using patients with PRO measurements at baseline and at least one post baseline measurement in the ITT population.

The scores of these EQ-5D-5L and FACT-Leu PRO questionnaires will be summarized using descriptive statistics (eg, mean and median) for each cohort by time point, overall, and for each dimension/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 (ie, 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; and a visual analog scale (VAS), where the same dimensions are rated along a 100-point visual ruler with 100 being best health.

The scores of these questionnaires rating HR-QoL for 5 dimensions and VAS will be summarized using descriptive statistics (ie, n, mean, SD, median, minimum and maximum) for each cohort.

The frequencies for each level of response for 5 dimensions will be summarized using categorical data analysis.

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 (ie, physical well-being, social/family well-being, emotional well-being, and functional well-being). A fifth category titled "Additional Concerns" contains general questions.

The scores of these questionnaires for 4 QoL domains and the fifth category titled "Additional Concerns" as well as LEU Subscale score, FACT-Leukemia TOI, Fact-G Total Score, FACT-Leukemia Total Score will be summarized using descriptive statistics (ie, n, mean, SD, median, minimum and maximum) for each cohort. Fact-G Total Score and FACT-Leukemia Total Score may be presented by graphs.

4.11 Interim Analysis

No efficacy interim analysis will be carried due to earlier termination of study accrual.

5 REFERENCES

Guidance for Industry Submission of Abbreviated Reports and Synopses in Support of Marketing Applications, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), August 1999

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6 APPENDIX

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	06-Aug-2020 22:46 UTC