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

NCT Number: NCT01207440

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STATISTICAL ANALYSIS PLAN

FOR

AP24534-10-201

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

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TABLE OF CONTENTS

LIST OF TABLES

1 INTRODUCTION

The AP24534-10-201 Statistical Analysis Plan describes the design characteristics and statistical analyses methods for study "A Pivotal Phase 2 Trial of Ponatinib (AP24534) in Patients with Refractory Chronic Myeloid Leukemia and Ph+ Acute Lymphoblastic Leukemia."

This document specifies the statistical approaches and data handling conventions for key analyses that include the primary analyses for the primary endpoints and the analyses for key secondary endpoints.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objectives

The primary objective of this trial is to determine the efficacy of ponatinib in patients with Chronic Myeloid Leukemia (CML) in chronic (CP), accelerated (AP) or blast phase (BP) or with Ph+ Acute Lymphoblastic Leukemia (ALL) who either are resistant or intolerant to either dasatinib or nilotinib or have the T315I mutation.

2.1.2 Secondary Objectives

Secondary objectives are:

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

2.2 Study Design

This is a phase 2, single-arm trial in patients with CML and Ph+ ALL. Table 1 summarizes the number of patients planned to be recruited in each cohort:

Table 1: Planned Number of Patients for Each Cohort

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

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

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

2.3 Study Endpoints

2.3.1 Primary Endpoints

The primary endpoints for the cohorts are:

Cohorts A and B (CP CML Patients)

- Major cytogenetic response (MCyR), defined as complete cytogenetic response (CCyR) or Partial Cytogenetic Response (PCyR). Patients entering the trial already in PCyR must achieve a CCyR in order to be considered as achieving a MCyR. The criteria for response are provided in Attachment A of the protocol.

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

- Major hematologic response (MaHR), defined as complete hematologic response (CHR) and no evidence of leukemia (NEL). MaHR will be confirmed by a peripheral blood complete blood count (CBC) and differential no earlier than 28 days after the initial assessment of MaHR. The criteria for response are provided in Attachment A of the protocol.

2.3.2 Secondary Endpoints

Secondary endpoints for this trial are:

- **Cohorts A and B:** CHR as defined in Attachment A of the protocol.
- **Cohorts C-F:** MCyR.
- Confirmed MCyR, defined as 2 assessments of CCyR or PCyR at least 28 days apart. For CP patients entering the trial in PCyR, confirmed MCyR will be defined as 2 assessments of CCyR at least 28 days apart.
- Major Molecular Response (MMR) (as defined in Attachment A of the protocol).
- Duration of Response, defined as the interval between the first assessment at which the criteria for response were met until the criteria for progression (as defined in Attachment A of the protocol) are met, censored at the last date at which the criteria for response are met. An additional analysis will be performed in which patients who do not progress will be censored at the last dose of study drug. Duration of response will also be defined and analyzed as the time from the first assessment at which the criteria for response are met until the last assessment at which the criteria for response are met.
- Progression free survival, defined as the interval from the first dose of study treatment until the criteria for progression are met (as defined in Attachment A of the protocol) or death, censored at the last response assessment.
- Overall survival, defined as the interval from the first dose of study treatment until death, censored at the last date at which patient was known to be alive.

- Time to response, defined as the interval from the first dose of study treatment until the criteria for response are first met, censored at the last assessment of response.

2.3.3 Exploratory Endpoints

Exploratory endpoints for this trial are:

CCI

[redacted]

3 ANALYSIS POPULATIONS

Each of the 6 cohorts will be analyzed separately. As stated in the protocol, patients will undergo testing at baseline for the presence of the T315I mutation via direct sequencing. The results of this test will determine the cohort to which a patient will ultimately be assigned.

For the purpose of statistical analyses, the following patient populations are defined for Cohorts A - F:

3.1 Treated Population

3.1.1 Cohorts A and B (CP CML Patients)

This population includes all patients assigned to Cohort A or B who have received at least 1 dose of study drug. Chronic phase patients for whom a negative baseline T315I mutation result is received and who are resistant or intolerant to either dasatinib or nilotinib will be assigned to Cohort A. Chronic phase patients for whom a positive baseline T315I mutation result is received will be assigned to Cohort B. Patients who are not confirmed to have a detectable T315I mutation by direct sequencing but who are not resistant or intolerant to dasatinib or nilotinib (ie, who have been treated with only imatinib) will not be included in the treated population (or the per protocol population described below) and will be analyzed separately. We estimate that approximately 20% of patients with a history of a T315I mutation will have been treated with only imatinib, and thus will not be resistant or intolerant to dasatinib or nilotinib, and about one-third of these patients will lack the mutation by direct sequencing. We also estimate that this situation will most likely apply to the CP candidates, as patients with AP, BP and Ph+ALL will most likely have received more extensive therapy. Thus, we estimate that approximately 10 patients will fall into this group.

3.1.2 Cohorts C-F (AP CML/BP CML/Ph+ ALL Patients)

This population includes all patients assigned to 1 of Cohorts C-F who have received at least 1 dose of study drug. CML patients in AP for whom a negative baseline T315I mutation result is received and who are resistant or intolerant to either dasatinib or nilotinib will be assigned to Cohort C. CML patients in AP for whom a positive baseline T315I mutation result is received will be assigned to Cohort D. CML patients in BP and Ph+ ALL patients for whom a negative baseline T315I mutation result is received and who are resistant or intolerant to either dasatinib

or nilotinib will be assigned to Cohort E. CML patients in BP and Ph+ ALL patients for whom a positive baseline T315I mutation result is received will be assigned to Cohort F. Patients who are not confirmed to have a detectable T315I mutation by direct sequencing and who are not resistant or intolerant to dasatinib or nilotinib will not be included in the treated population and will be analyzed separately, in the same fashion as described for Cohorts A and B.

3.2 Per Protocol Population

3.2.1 Per Protocol (Cytogenetic) Population

This population includes all patients in the treated population who have a baseline cytogenetic assessment with at least 20 metaphases examined. For Cohorts A and B (CP CML Patients), the primary analysis will be performed using the per protocol (cytogenetic) population. For Cohorts C-F (AP CML/BP CML/Ph+ ALL Patients), the analysis of the secondary endpoint of MCyR will be peformed using the per protocol (cytogenetic) population.

3.2.2 Per Protocol (Hematologic) Population

This population includes all patients in the treated population in Cohorts C-F who have a baseline BM assessment for which the percentage of BM blasts can be determined. For Cohorts C-F (AP CML/BP CML/Ph+ ALL Patients), the primary analysis will be performed using the per protocol (hematologic) population.

3.3 Safety Population

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

4 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

4.1 Determination of Sample Size

4.1.1 Cohorts A and B (Chronic Phase CML Patients)

As specified in Section 2.3, the primary endpoint for this trial for patients with CP CML (Cohorts A and B) is MCyR. MCyR rate is defined as the proportion of patients who have achieved a CCyR or PCyR after the initiation of study treatment. Patients entering the trial already in PCyR must achieve a CCyR in order to be considered as achieving a MCyR. As described above, the determination of PCyR status at baseline for the primary analysis will be based on an assessment with an examination of at least 20 metaphases.

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

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

(resistant and intolerant CP patients). Here, and with regard to the cohorts discussed below, we intend that the specified null or uninteresting response rate defines a result that would not be clinically useful for the patient populations for which it is applicable. The alternative MCyR rate is set at 35% for Cohort A. The clinical implication of the alternative rate, in contrast, is that it would compare favorably with the historical experience for the specified patient populations and thus would be clinically beneficial. The overall alpha level for each cohort will be set at 0.05. With a cohort size of 100 patients, a minimum of 29 responders (ie, those with a CCyR and a PCyR) would need to be observed in Cohort A in order to observe an exact 95% CI such that the lower bound exceeds 20% and the upper bound exceeds 35%. Therefore, 100 patients will provide at least 85% power to distinguish between a null response rate of 20% and an alternative response rate of 35% in Cohort A. The study will also provide at least 98% power to distinguish between 20% and 40%, in which case 29 responses will also be required, and at least 78% power to distinguish between 30% and 45%, in which case 40 responses would be required.

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

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

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

4.1.2 Cohorts C-F (Accelerated Phase CML/Blast Phase CML/Ph+ ALL Patients)

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

The sample size considerations for each cohort are summarized in Table 2:

Table 2: Sample Size Considerations for Each Cohort

COHORT	Disease Phase	Eligibility Criterion	Primary Endpoint	Sample Size	Effect Size	Power
A	CP	R/I	MCyR	100	35% vs. 20% 40% vs. 20% 45% vs. 30%	≥85% ≥98% ≥78%
B	CP	T315I	MCyR	60	35% vs 10% 25% vs. 10%	98% 85%
C	AP	R/I	MaHR	40	30% vs. 10%	90%
D	AP	T315I	MaHR	40	30% vs. 10%	90%
E	BP/Ph+ALL	R/I	MaHR	40	30% vs. 10%	90%
F	BP/Ph+ALL	T315I	MaHR	40	30% vs. 10%	90%

CP = chronic phase, R/I = resistance and/or intolerant, MCyR = major cytogenetic response, AP = accelerated phase, MaHR = major hematologic response, BP = blast phase, Ph+ ALL, Philadelphia chromosome positive acute lymphoblastic leukemia.

4.2 Statistical Methods

4.2.1 Demographic and Baseline Characteristics

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

4.2.2 Patient Disposition

Patient disposition will be summarized separately for each cohort. Table 3 below describes the anticipated presentation of key patient disposition categories for each cohort:

Table 3: Patient Disposition

	Treated Patients (N=)
Patients still on therapy	
Patients discontinued from therapy:	
In survival follow-up	
Died	
Lost to follow-up	
Withdrew consent	
Primary reason for discontinuation	
Progressive Disease	
Adverse Event	
Death	
Consent withdrawn	
Noncompliance with study drug	
Protocol violation	
Physician decision	
Lack of Efficacy	
Lost to follow-up	
Pregnancy	
Withdrawal by subject	
Other	

4.2.3 Efficacy Analyses

4.2.3.1 Primary Analysis of the Primary Endpoint

Cohorts A and B (CP CML Patients)

As specified in Section 2.3, the primary endpoint for patients with CP CML in Cohorts A and B is MCyR. MCyR rate is defined as the proportion of patients who have achieved a CCyR or PCyR after the initiation of study treatment. Patients entering the trial in PCyR must achieve a CCyR in order to be considered as achieving a MCyR. Specifically, Table 4 summarizes how patient MCyR status will be classified based on baseline cytogenetic assessment:

Table 4: MCyR Classification and Baseline Cytogenetic Assessment

	On-Study Assessment		
Baseline Assessment	PCyR	CCyR	Less than PCyR
Less than PCyR	**MCyR**	**MCyR**	No MCyR
PCyR	No MCyR	**MCyR**	No MCyR

PCyR = partial cytogenetic reponse, CCyR = complete cytogenetic response, MCyR = major cytogenetic response.

The primary analysis of the primary endpoint will be performed using an exact 95% CI for the MCyR rate, using the per protocol (cytogenetic) population for each cohort. Patients who do not meet the criteria for MCyR will be analyzed as non-successes.

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

The primary endpoint for patients with AP or BP CML or patients with Ph+ ALL in Cohorts C – F is MaHR. MaHR rate is defined as the proportion of patients who have achieved a CHR or NEL response after the initiation of study treatment.

The primary analysis of the primary endpoint will be performed using an exact 95% CI for the MaHR rate using the per protocol (hematologic) population for each cohort. Patients who do not meet the criteria for MaHR will be analyzed as non-successes.

All Cohorts

In the event of over-enrollments beyond 10% of the planned sample size, a sensitivity analysis will be performed on the per protocol population when the sample size requirement is first realized.

The 6 cohorts will be analyzed separately and no adjustments for multiplicity are planned.

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

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

- All CP CML patients (Cohorts A and B) will have an opportunity to demonstrate MCyR up to 12 months after initiation of study treatment. Patients in Cohorts A and B who do not respond by 12 months after the initiation of study treatment will be analyzed as non-successes.
- All AP/BP phase CML patients and Ph+ ALL patients (Cohorts C, D, E and F) will have an opportunity to demonstrate MaHR up to 6 months after initiation of study treatment. Patients

in Cohorts C-F who do not respond by 6 months after the initiation of study treatment will be analyzed as non-successes.

- For patients entering the trial in less than PCyR, determination of MCyR requires a cytogenetic assessment with at least 13 metaphases examined:
    - If 20 or more metaphases are examined, determination of MCyR will be based on the %Ph+ cells as specified in Attachment A of the protocol.
    - If 13-19 metaphases are examined, determination of MCyR will be performed as follows:

Table 5: Determination of PCyR With Assessment of < 20 Metaphases

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

*The minimum of 13 metaphases is based on the threshold for MCyR of 7 Ph+ cells out of 20 metaphases.

- For patients entering the trial in PCyR, a CCyR must be observed in order to meet the criteria for MCyR; therefore, determination of MCyR requires a cytogenetic assessment with at least 20 metaphases examined.
- The criteria for initial determination of MaHR require the following sources of data:
    - BM Aspirate,
    - CBC with Differential,
    - Physical Exam.

  In order to meet the criteria for MaHR, the above assessments must be performed within 14 days of one another. At assessments subsequent to the assessment at which the criteria for MaHR are first met, a physical exam is not required.
- Initial determination of MaHR must be confirmed no earlier than 28 days later; this confirmation requires the following source of data:
    - CBC with Differential.

4.2.3.3 Sensitivity Analyses of the Primary Endpoint

Two additional sensitivity analyses of the primary endpoint will be performed as follows:

Sensitivity Analysis 1

Sensitivity Analysis 1 is intended to assess the impact of the use of the per protocol population and the timing of when patients first demonstrate the criteria for success.

- Analysis of the primary endpoint will be performed on the treated population as specified in Section 3.
- For analyses of MCyR (primary endpoint for Cohorts A and B), all patients in the treated population will be included, regardless of the number of metaphases examined for the baseline cytogenetic assessment.
- The determination of PCyR status at baseline will be based on the percentage of Ph+ cells, regardless of the number of metaphases examined.
- Determination of success/not a success will be based on all available data in the database, regardless of when the criteria for success are met.

Sensitivity Analysis 2

Sensitivity Analysis 2 is intended to assess the impact of patients for whom the baseline T315I direct sequencing result is not received until after the first bone marrow assessment.

- Patients for whom a **positive** baseline T315I direct sequencing result is received after the first cytogenetic response assessment (CML patients in CP) or BM assessment (CML patients in AP or BP and Ph+ ALL patients) will be analyzed as T315I-.
- Patients for whom a **negative** baseline T315I direct sequencing result is received after first cytogenetic response assessment (CML patients in CP) or BM assessment (CML patients in AP or BP and Ph+ ALL patients) will be analyzed as T315I+.
- For analyses of MCyR (primary endpoint for Cohorts A and B), all patients in the treated population will be included, regardless of the number of metaphases examined for the baseline cytogenetic assessment.
- The determination of PCyR status at baseline will be based on the percentage of Ph+ cells, regardless of the number of metaphases examined.
- Determination of success/not a success will be based on all available data in the database, regardless of when the criteria for success are met.

4.2.4 Key Analyses of the Secondary Endpoints

The key analyses of the secondary endpoints are specified below. Data handling rules for these analyses are specified in Section 4.2.4.4

4.2.4.1 Cohorts A and B (CP CML Patients)

- CHR: the CHR rate is defined as the proportion of patients who have achieved a CHR after the initiation of study treatment. Chronic phase CML patients entering the trial in CHR will be excluded from this analysis. The analysis will be performed using a 2-sided exact 95% CI for the CHR rate.

4.2.4.2 Cohorts C-F (AP CML/BP CML/Ph+ ALL Patients)

- MCyR: the MCyR rate is defined as the proportion of patients who have achieved a CCyR or PCyR after the initiation of study treatment. The analysis will be performed using a 2-sided exact 95% CI for the MCyR rate, using the per protocol population.

4.2.4.3 All Cohorts

- Confirmed MCyR: the confirmed MCyR rate is defined as the proportion of patients who have achieved a confirmed CCyR or PCyR after the initiation of study treatment. Patients entering the trial already in PCyR must achieve a confirmed CCyR in order to be considered a success for the confirmed MCyR rate. The analysis will be performed using a 2-sided exact 95% CI for the confirmed MCyR rate.
- Duration of response will be estimated using the Kaplan-Meier method. The median duration of response and 95% CI will be calculated. An additional analysis will be performed defining the duration as the time from the first assessment at which the criteria for response are met until the last assessment at which the criteria for response are met. Duration of response will be analyzed for MCyR, MaHR (Cohorts C-F), CHR (Cohorts A and B), and MMR.
- Progression-free survival, overall survival and time to response will be estimated using the Kaplan-Meier method. The median progression-free survival, overall survival, and time to response and 95% CI will be calculated.
- Major molecular response rate will be defined as the proportion of patients who meet the criteria for MMR at least once after the initiation of study treatment. The analysis will be performed using a 2-sided exact 95% CI for the MMR rate.

4.2.4.4 Data Handling Rules for Secondary Endpoint Analyses

In addition to the data handling rules specified in Section 4.2.3.2, the following key data handling rules for the secondary efficacy analyses will be implemented (note that the definition of progression is specified in Attachment A of the protocol).

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

defined as more than 182 days between consecutive visits; for Cohorts C-F, 2 missed visits will be defined as more than 126 days between consecutive visits.

- Determination of MMR will be based on BCR-ABL and ABL reversed transcribed transcript levels in peripheral blood assessments for Cohorts A-F and BM assessments for Cohorts E and F (BP CML/Ph+ ALL Patients). MMR will be determined only for patients with the b2a2/b3a2 variant of BCR-ABL.

4.3 Summaries of Data Handling Rules for Primary and Secondary Efficacy Analyses

Table 6: Summary of Data Handling Rules for Major Cytogenetic Response (MCyR)

Note: all assessments must be after the initiation of study treatment unless otherwise specified.

	PRIMARY ANALYSIS	SENSITIVITY ANALYSIS 1	SENSITIVITY ANALYSIS 2
Population	**Per Protocol (Cytogenetic) Population**	**Treated Population** (includes patients with < 20 metaphases examined for baseline cytogenetic assessment)	**Treated Population** (includes patients with < 20 metaphases examined for baseline cytogenetic assessment) • Patients for whom a **positive** baseline T315I direct sequencing result is received after the first cytogenetic response assessment (CML patients in CP) or BM assessment (CML patients in AP or BP and Ph+ ALL patients) will be analyzed as **T315I-**. • Patients for whom a **negative** baseline T315I direct sequencing result is received after first cytogenetic response assessment (CML patients in CP) or BM assessment (CML patients in AP or BP and Ph+ ALL patients) will be analyzed as **T315I+.**
MCyR	**For patients not in PCyR at study entry (>35% Ph+ cells):** 1 assessment of: • 0-35% Ph+ cells with at least 20 metaphases examined **OR** • See Table 5 **For patients in PCyR at study entry (>0% and ≤35% Ph+ cells):** 1 assessment of 0% Ph+ cells with at least 20 metaphases examined ≤ 12 months after initiation of study treatment	**For patients not in PCyR at study entry (>35% Ph+ cells):** 1 assessment of: • 0-35% Ph+ cells with at least 20 metaphases examined **OR** • See Table 5 **For patients in PCyR at study entry (>0% and ≤35% Ph+ cells):** 1 assessment of 0% Ph+ cells with at least 20 metaphases examined Any time after initiation of study treatment	**For patients not in PCyR at study entry (>35% Ph+ cells):** 1 assessment of: • 0-35% Ph+ cells with at least 20 metaphases examined **OR** • See Table 5 **For patients in PCyR at study entry (>0% and ≤35% Ph+ cells):** 1 assessment of 0% Ph+ cells with at least 20 metaphases examined Any time after initiation of study treatment

	PRIMARY ANALYSIS	SENSITIVITY ANALYSIS 1	SENSITIVITY ANALYSIS 2
Confirmed MCyR	**For patients not in PCyR at study entry (>35% Ph+ cells):** 2 consecutive assessments at least 4 weeks apart of: • 0-35% Ph+ cells with at least 20 metaphases examined **OR** • See Table 5 **For patients in PCyR at study entry:** 2 consecutive assessments at least 4 weeks apart of 0% Ph+ cells with at least 20 metaphases examined ≤ 12 months after initiation of study treatment	**For patients not in PCyR at study entry (>35% Ph+ cells):** 2 consecutive assessments at least 4 weeks apart of: • 0-35% Ph+ cells with at least 20 metaphases examined **OR** • See Table 5 **For patients in PCyR at study entry**: 2 consecutive assessments at least 4 weeks apart of 0% Ph+ cells with at least 20 metaphases examined Any time after initiation of study treatment	**For patients not in PCyR at study entry (>35% Ph+ cells):** 2 consecutive assessments at least 4 weeks apart of: • 0-35% Ph+ cells with at least 20 metaphases examined **OR** • See Table 5 **For patients in PCyR at study entry:** 2 consecutive assessments at least 4 weeks apart of 0% Ph+ cells with at least 20 metaphases examined Any time after initiation of study treatment

Table 7: Summary of Data Handling Rules for Major Hematologic Response (MaHR)

	PRIMARY ANALYSIS	SENSITIVITY ANALYSIS 1	SENSITIVITY ANALYSIS 2
Population	**Per Protocol (Hematologic) Population**	**Treated Population** (includes patients with baseline bone marrow assessments for which percent blast cannot be determined)	**Treated Population** (includes patients with baseline bone marrow assessments for which percent blast cannot be determined) • Patients for whom a **positive** baseline T315I direct sequencing result is received after the first cytogenetic response assessment (CML patients in CP) or BM assessment (CML patients in AP or BP and Ph+ ALL patients) will be analyzed as **T315I-.** • Patients for whom a **negative** baseline T315I direct sequencing result is received after first cytogenetic response assessment (CML patients in CP) or BM assessment (CML patients in AP or BP and Ph+ ALL patients) will be analyzed as **T315I+**.
MaHR (CHR)	1 assessment at which all of the following criteria are met: • WBC ≤ ULN • ANC ≥ 1000/mm^3 • Platelets ≥ 100,000/mm^3 • No blasts or promyelocytes in peripheral blood • BM blasts ≤ 5% • < 5% myelocytes plus metamyelocytes in peripheral blood • Basophils in peripheral blood < 5% • No extramedullary involvement (including no hepatomegaly or splenomegaly) ≤ 6 months after initiation of study treatment	1 assessment at which all of the following criteria are met: • WBC ≤ ULN • ANC ≥ 1000/mm^3 • Platelets ≥ 100,000/mm^3 • No blasts or promyelocytes in peripheral blood • BM blasts ≤ 5% • < 5% myelocytes plus metamyelocytes in peripheral blood • Basophils in peripheral blood < 5% • No extramedullary involvement (including no hepatomegaly or splenomegaly) Any time after initiation of study treatment	1 assessment at which all of the following criteria are met: • WBC ≤ ULN • ANC ≥ 1000/mm^3 • Platelets ≥ 100,000/mm^3 • No blasts or promyelocytes in peripheral blood • BM blasts ≤ 5% • < 5% myelocytes plus metamyelocytes in peripheral blood • Basophils in peripheral blood < 5% • No extramedullary involvement (including no hepatomegaly or splenomegaly) ≤ 6 months after initiation of study treatment

	PRIMARY ANALYSIS	SENSITIVITY ANALYSIS 1	SENSITIVITY ANALYSIS 2
	1 additional assessment at which all of the following criteria are met, at least 28 days after the first assessment of response: • WBC ≤ ULN • ANC ≥ 1000/mm^3 • Platelets ≥ 100,000/mm^3 • No blasts or promyelocytes in peripheral blood • < 5% myelocytes plus metamyelocytes in peripheral blood • Basophils in peripheral blood < 5%*	1 additional assessment at which all of the following criteria are met, at least 28 days after the first assessment of response: • WBC ≤ ULN • ANC ≥ 1000/mm^3 • Platelets ≥ 100,000/mm^3 • No blasts or promyelocytes in peripheral blood • < 5% myelocytes plus metamyelocytes in peripheral blood • Basophils in peripheral blood < 5%*	1 additional assessment at which all of the following criteria are met, at least 28 days after the first assessment of response: • WBC ≤ ULN • ANC ≥ 1000/mm^3 • Platelets ≥ 100,000/mm^3 • No blasts or promyelocytes in peripheral blood • < 5% myelocytes plus metamyelocytes in peripheral blood • Basophils in peripheral blood < 5%*
MaHR (NEL)	1 assessment at which all of the following criteria are met: • WBC ≤ ULN • No blasts or promyelocytes in peripheral blood • BM blasts ≤ 5% • < 5% myelocytes plus metamyelocytes in peripheral blood • Basophils in peripheral blood < 5% • No extramedullary involvement (including no hepatomegaly or splenomegaly) • At least 1 of the following: (i) 20,000/mm^3 ≤ platelets < 100,000/mm^3; (ii) 500/mm^3 ≤ ANC <1000/mm^3 ≤ 6 months after initiation of study treatment 1 additional assessment at which all of the following criteria are met, at least 28 days after the first assessment of response:	1 assessment at which all of the following criteria are met: • WBC ≤ ULN • No blasts or promyelocytes in peripheral blood • BM blasts ≤ 5% • < 5% myelocytes plus metamyelocytes in peripheral blood • Basophils in peripheral blood < 5% • No extramedullary involvement (including no hepatomegaly or splenomegaly) • At least 1 of the following: (i) 20,000/mm^3 ≤ platelets < 100,000/mm^3; (ii) 500/mm^3 ≤ ANC <1000/mm^3 Any time after initiation of study treatment 1 additional assessment at which all of the following criteria are met, at least 28 days after the first assessment of response:	1 assessment at which all of the following criteria are met: • WBC ≤ ULN • No blasts or promyelocytes in peripheral blood • BM blasts ≤ 5% • < 5% myelocytes plus metamyelocytes in peripheral blood • Basophils in peripheral blood < 5% • No extramedullary involvement (including no hepatomegaly or splenomegaly) • At least 1 of the following: (i) 20,000/mm^3 ≤ platelets < 100,000/mm^3; (ii) 500/mm^3 ≤ ANC <1000/mm^3 ≤ 6 months after initiation of study treatment 1 additional assessment at which all of the following criteria are met, at least 28 days after the first assessment of response:

	PRIMARY ANALYSIS	SENSITIVITY ANALYSIS 1	SENSITIVITY ANALYSIS 2
	• WBC ≤ ULN • No blasts or promyelocytes in peripheral blood • < 5% myelocytes plus metamyelocytes in peripheral blood • Basophils in peripheral blood < 5% • At least 1 of the following: (i) 20,000/mm^3 ≤ platelets < 100,000/mm^3; (ii) 500/mm^3 ≤ ANC <1000/mm^3	• WBC ≤ ULN • No blasts or promyelocytes in peripheral blood • < 5% myelocytes plus metamyelocytes in peripheral blood • Basophils in peripheral blood < 5% • At least 1 of the following: (i) 20,000/mm^3 ≤ platelets < 100,000/mm^3; (ii) 500/mm^3 ≤ ANC <1000/mm^3	• WBC ≤ ULN • No blasts or promyelocytes in peripheral blood • < 5% myelocytes plus metamyelocytes in peripheral blood • Basophils in peripheral blood < 5% • At least 1 of the following: (i) 20,000/mm^3 ≤ platelets < 100,000/mm^3; (ii) 500/mm^3 ≤ ANC <1000/mm^3

*Refer to protocol amendment 1; basophils in peripheral blood changed from <20% to <5%.

Table 8: Summary of Data Handling Rules for Analysis of Duration of Response†

CONDITION	ANALYSIS 1	ANALYSIS 2	ANALYSIS 3	ANALYSIS 4 (Duration of Confirmed Response)
No progression or loss of response	Censored at last date patient met criteria for response	Censored at date of last dose of study drug	Censored at date of last dose of study drug	Censored at last date patient met criteria for response
Progression or loss of response* any time after a single (unconfirmed) assessment of response	Progression (Duration = Date of relapse – Date of first response assessment)	Progression (Duration = Date of relapse – Date of first response assessment)	Progression (Duration = Date of relapse – Date of first response assessment)	Excluded
Progression or loss of response any time after two consecutive assessments of response at least 4 weeks apart (confirmation of response)	Progression (Duration = Date of relapse – Date of first response assessment)	Progression (Duration = Date of relapse – Date of first response assessment)	Progression (Duration = Date of relapse – Date of first response assessment)	Progression (Duration = Date of relapse – Date of second response assessment)
Progression or loss of response after one missed or incomplete assessment	Progression (Duration = Date of relapse – Date of first response assessment)	Progression (Duration = Date of relapse – Date of first response assessment)	Progression (Duration = Date of relapse – Date of first response assessment)	Censored at last date patient met criteria for response
Progression or loss of response after two or more missed or incomplete assessments	Censored at last date patient met criteria for response	Censored at date of last dose of study drug	Progression (Duration = Date of relapse – Date of first response assessment)	Censored at last date patient met criteria for response
Initiation of prohibited anti-leukemia therapy (including stem cell transplant) prior to loss of unconfirmed response	Censored at date of initiation of new therapy	Censored at date of initiation of new therapy	Censored at date of initiation of new therapy	Excluded
Initiation of prohibited anti-leukemia therapy (including stem cell transplant) prior to loss of confirmed response	Censored at date of initiation of new therapy	Censored at date of initiation of new therapy	Censored at date of initiation of new therapy	Censored at last date patient met criteria for response

CONDITION	ANALYSIS 1	ANALYSIS 2	ANALYSIS 3	ANALYSIS 4 (Duration of Confirmed Response)
Cohorts A and B: Failure to respond by 12 months after the initiation of study treatment **Cohorts C, D, E, and F:** Failure to respond by 6 months after the initiation of study treatment	Excluded	Excluded	Included if patient meets criteria for response	Excluded

† An additional analysis will be performed defining the duration as the time from the first assessment at which the criteria for response are met until the last assessment at which the criteria for response are met.

Table 9: Summary of Data Handling Rules for Analysis of Major Molecular Response (MMR)

CONDITION	ANALYSIS 1	ANALYSIS 2	ANALYSIS 3
No baseline result obtained	Non-success	Excluded	Analyze as observed
MMR at baseline	Non-success	Excluded	Analyze as observed
Detectable levels of BCR-ABL and ABL at baseline followed by Not Detectable levels of BCR-ABL post-baseline	Success	Success	Success
Measurement of BCR-ABL or ABL considered to be aberrant upon medical review	Data point will be used for determination of MMR	Data point will be excluded for determination of MMR	Data point will be excluded for determination of MMR

4.3.1 Subgroup Analyses of the Primary Endpoints and Key Secondary Endpoints

For the primary endpoint and selected key secondary endpoints, subgroup analyses will be performed by key baseline potential prognostic factors. Subgroups will include:

- Age
- Gender
- Race
- Eastern Cooperative Oncology Group (ECOG) performance status
- Geographic Region (US vs. Rest of World [ROW])
- Time Since Diagnosis
- Mutation Status
    - Via Direct Sequencing method
        - T315I mutation
        - Kinase Domain (KD) mutations other than T315I
        - No detectable KD mutations
    - Via allele-specific oligonucleotide (ASO) method
        - T315I+ vs. T315I-
    - T315I status by history
        - T315+ vs. T315I-
- Prior TKI Exposure
    - 2^{nd} line (1 prior TKI) vs. 3^{rd} line (any 2 prior TKIs) vs. $>3^{rd}$ line (any 3 or more prior TKIs)
    - Nilotinib Exposure (Yes/No)
    - Dasatinib Exposure (Yes/No)
    - Intolerant vs. Resistant (to Dasatinib or Nilotinib)
- BCR-ABL/ABL transcript ratio
- PCyR at baseline
- High-enrolling investigational sites (if applicable)
- Other Disease-Related Prognostic Factors
- T315I and Resistant-Intolerant patients will be pooled within disease groups where applicable (eg, pooling of Cohorts A and B)

4.3.2 Treated Patients Not Eligible for Cohorts A-F

Patients who receive study treatment but who are not confirmed to have a detectable baseline T315I mutation by direct sequencing and who are not resistant or intolerant to dasatinib or nilotinib will be analyzed separately according to the data handling rules for primary and secondary efficacy analyses, if applicable.

4.3.3 Safety Analyses

All safety analyses will be performed on the safety population, which will include all patients who have received at least one dose of study drug. The safety data from all cohorts will be pooled.

The adverse event incidence rates, as well as the frequency of occurrence of overall toxicity categorized by toxicity grades (severity), will be described. All adverse events starting on or

after the first dose of study treatment will be considered treatment-emergent. In addition, adverse events will be summarized by relatedness to study treatment (in the opinion of the investigator) and action taken with study treatment, including dose modifications, interruptions and discontinuation. Serious adverse events, both overall and by relationship to study treatment, will also be summarized.

Laboratory data results will be standardized and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE, v.4.0) criteria when applicable. Change from baseline to the worst on-study result will be summarized for these standardized results. Listings of laboratory test results will also be generated for all laboratory data collected.

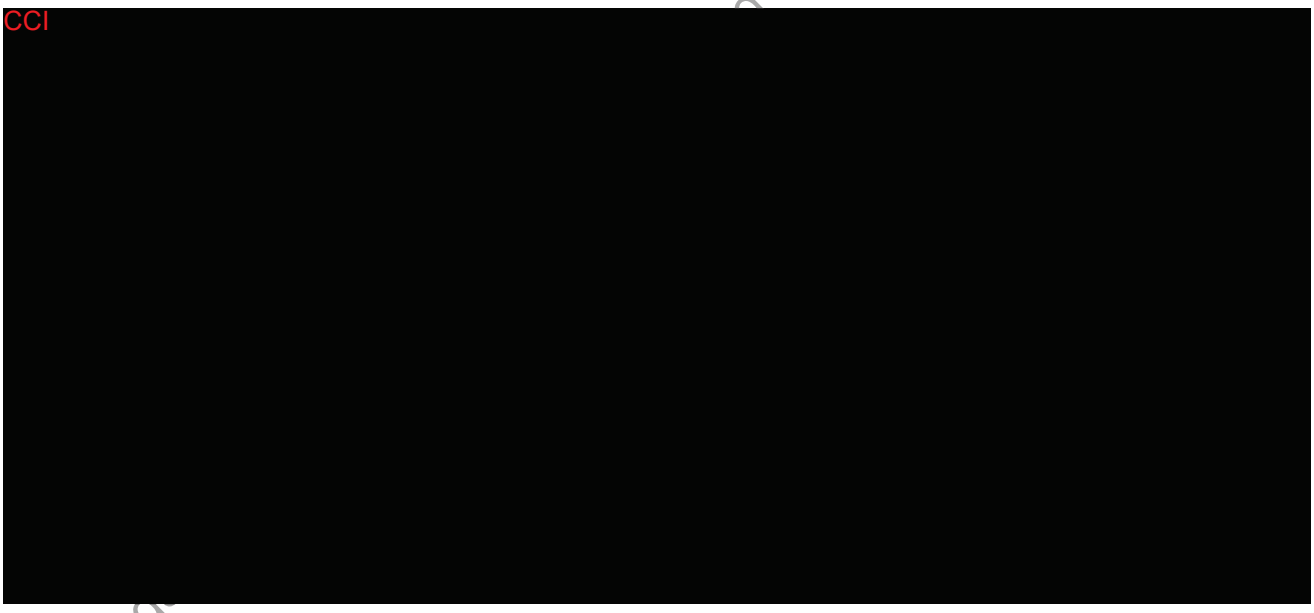
4.3.4 Study Drug Exposure

Parameters pertaining to study drug exposure (number of doses, cumulative dose, days from first dose to last dose) will be summarized separately for each cohort. Compliance will also be summarized, including percent compliance, and number of patients with a dose delay or dose reduction.

4.3.5 Exploratory Analyses

The following exploratory analyses will be performed:

CCI



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