Title: A Phase I/II Multi-center, Open-label Study of Ponatinib in Japanese Patients with Chronic Myeloid Leukemia (CML) who have failed Dasatinib or Nilotinib or Ph+ Acute Lymphoblastic Leukemia (ALL) who have failed Prior Tyrosine Kinase Inhibitors (TKIs)

NCT Number: NCT01667133

SAP Approve Date: 04 March 2015

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Statistical Analysis Plan

PROTOCOL TITLE: A Phase I/II Multi-center, Open-label Study of Ponatinib in Japanese Patients with Chronic Myeloid Leukemia (CML) who have failed Dasatinib or Nilotinib or Ph+ Acute Lymphoblastic Leukemia (ALL) who have failed Prior Tyrosine Kinase Inhibitors (TKIs)

PROTOCOL NUMBER: AP24534-11-106

PROTOCOL DATE:

SAP VERSION: Version 1.0

DATE: 04 March 2015

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1 INTRODUCTION

1.1 Statistical Analysis Plan

This document is the Statistical Analysis Plan (SAP) containing definitions and descriptions of statistical analysis procedures for "A phase I/II multi-center, open-label study of ponatinib in Japanese patients with chronic myeloid leukemia (CML) who have failed dasatinib or nilotinib or Ph+ acute lymphoblastic leukemia (ALL) who have failed prior tyrosine kinase inhibitors (TKIs) (protocol number: AP24534-11-106)".

1.2 Study Objectives

1.2.1 Primary Objectives

- The primary objective of the phase I component is to examine the safety of the recommended dose of oral ponatinib in Japanese patients with CML, who are resistant or intolerant to dasatinib or nilotinib or Ph+ ALL, who are resistant or intolerant to prior TKIs.
- The primary objective of the phase II component is to confirm the anti-leukemic activity of ponatinib in Japanese patients with CML, who are resistant or intolerant to dasatinib or nilotinib or Ph+ ALL, who are resistant or intolerant to prior TKIs as evidenced by clinical responses, molecular responses, and clinical outcomes.

1.2.2 Secondary Objectives

The secondary objectives of this study are:

- To examine the PK of ponatinib in Japanese patients with CML who are resistant or intolerant to dasatinib or nilotinib or Ph+ ALL, who are resistant or intolerant to prior TKIs.
- To describe potential pharmacogenomic markers of ponatinib anti-leukemic activity and to characterize the molecular status of patients.

1.3 Modifications from the Protocol

N/A

2 SOFTWARE AND DICTIONARIES

2.1 Statistical Analysis and Tabulation Software

Table 1 Software and Versions Used in this Study

	Software and Versions
OS	Microsoft Windows XP
Statistical Analysis Software	SAS V.9.2
Tabulation Software	Microsoft Word and Excel 2010
WinNonlin	WinNonlin Ver. 6.1 or later

2.2 Dictionaries

Table 2 Dictionaries Used in this Study

Category	Dictionary	Remarks
Adverse Events	MedDRA version 17 or the latest Version	For adverse event summary tables, System Organ Class and preferred term will be applied, and the version of MedDRA will be provided. Unless otherwise specified, output tables will be sorted by descending number of subjects and alphabetical order for preferred terms.
Name of Medication (Concomitant Drugs)	WHODDB3E Sept 2011	Use the PN codes.
Laboratory Data	NCI CTCAE Version 4.0	For some laboratory tests, grade will be ranked according to CTCAE.

3 DEFINITION OF TERMS

3.1 Patient Groups

For the Phase I portion, analysis for the phase II dose determination is basically performed by each initial dose level (30 mg and 45 mg). For the Phase II portion, efficacy and safety analyses include all patients treated in this study using data collected in both portions. Analysis is basically performed for each disease group (CP-CML, AP-CML, BP-CML, and Ph+ ALL) and a pooled group of the advanced phases (AP-CML, BP-CML, and Ph+ ALL). The primary analysis of the primary endpoints and selected secondary endpoints is also performed for dose cohorts formed according to initial dose: 30 mg, 15/45 mg. The patient groups are defined in the Table 3.

Table 3 Definition of Patient Groups

Phase	Definitions
Phase I Portion	- 30 mg cohort: Patients initially treated with 30 mg ponatinib - 45 mg cohort: Patients initially treated with 45 mg ponatinib
Phase II Portion By Disease	- CP-CML: Treated patients with CP-CML (data in the phase 1 portion is included) - AP-CML: Treated patients with AP-CML (data in the phase 1 portion is included) - BP-CML: Treated patients with BP-CML (data in the phase 1 portion is included) - Ph+ ALL: Treated patients with Ph+ ALL (data in the phase 1 portion is included) - Pooled AP-CML, BP-CML, and Ph+ ALL group: Treated patients with AP-CML, BP-CML or Ph+ ALL (data in the phase 1 portion is included) - All treated patients (data in the phase 1 portion is included)
Phase II Portion By Initial Dose	- 30 mg: Patients initially treated with 30 mg ponatinib (data in the phase 1 portion is included) - 15/45 mg: Patients initially treated with 15 mg or 45 mg ponatinib (data in the phase 1 portion is included) - All treated patients (data in the phase 1 portion is included)

3.2 Efficacy Assessment

3.2.1 Primary Endpoints

Phase I:

Safety of the recommended dose of oral ponatinib in Japanese patients with CML who are resistant or intolerant to dasatinib or nilotinib or Ph+ ALL, who are resistant or intolerant to prior TKIs.

Phase II:

For CML patients in CP at study entry: Major cytogenetic response (MCyR), defined as complete cytogenetic response (CCyR) or partial cytogenetic response (PCyR). CP patients in CCyR are not eligible for this study. Patients entering the trial already in PCyR must achieve a CCyR in order to be considered as achieving an MCyR. The criteria for response are provided in Appendix A of the protocol.

For CML patients in AP, BP, or Ph+ ALL at study entry: Major hematologic response (MaHR), defined as complete hematologic response (CHR) or no evidence of leukemia (NEL). AP, BP, and Ph+ ALL patients in MaHR are not eligible for this study. 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 Appendix A of the protocol.

3.2.2 Secondary Endpoints

For CML patients in CP:

- Hematologic responses: Complete hematologic response (CHR). The criteria for CHR are provided in Appendix A of the protocol.
- Cytogenetic responses: 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.
- Molecular responses: Major molecular response (MMR). The criteria for MMR are provided in Appendix A of the protocol.

For CML patients in AP, BP, or Ph+ ALL patients:

- Cytogenetic responses: CCyR, PCyR, confirmed MCyR. Confirmed MCyR is defined as 2 assessments of CCyR or PCyR at least 28 days apart. For patients entering the trial in PCyR, confirmed MCyR will be defined as 2 assessments of CCyR at least 28 days apart.
- Molecular responses: MMR. The criteria for MMR are provided in Appendix A of the protocol.

For all patients:

Time to response, duration of response, progression-free survival, and overall survival.

3.2.3 Exploratory Endpoints

- CCI
- [redacted]

3.3 Safety Assessment

3.3.1 Adverse Events/Drug Related Adverse Events

Table 4 Definitions of AE and Causal Relationship to the Study Drug

Term	Definition
AE (Adverse Event)	An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product whether or not considered related to the medicinal product. Any worsening of a preexisting condition, which is temporally associated with the use of the study drug (ie, occurs after the first dose of study drug), is also an AE.
Drug Related Adverse Event	The Investigator will use medical consideration and use the following categories of causality to determine the relatedness of an AE with the study drug based on the following definitions: • Definitely Not Related (not drug related) • Probably Not Related (not drug related) • Possibly Related (drug related) • Probably Related (drug related) • Definitely Related (drug related) "Possibly Related", "Probably Related", "Definitely Related" AEs are defined as Drug Related AEs.

3.3.2 Laboratory Test Results and Vital Signs

Table 5 Laboratory Test Results and Vital Signs Evaluated in This Study

Classification	Examination Component	Unit	Rounding Digit
Hematology	White Blood Cell count	x10^9/L	0.01
	Lymphocyte	%	0.1
	Monocyte	%	0.1
	Eosinophil	%	0.1
	Basophil	%	0.1
	Neutrophil	%	0.1
	Neutrophil count	x10^9/L	0.1
	Lymphocyte count	x10^9/L	0.1
	Monocyte count	x10^9/L	0.1
	Eosinophil count	x10^9/L	0.1
	Basophil count	x10^9/L	0.1
	Hemoglobin	g/L	1
	Hematocrit	%	0.001
	Platelet count	x10^9/L	1
	Absolute neutrophil count (ANC)	x10^9/L	0.001
	Metamyelocytes	%	0.1
	Promyelocytes	%	1
	Myelocytes	%	0.01
	Blasts	%	0.1
	Bands	%	0.1
	Atypical Lymphocytes	%	0.1
	Metamyelocytes count	x10^9/L	0.1
	Promyelocytes count	x10^9/L	0.1
	Myelocytes count	x10^9/L	0.1
	Blasts count	x10^9/L	0.1
	Bands count	x10^9/L	0.1
	Atypical Lymphocytes count	x10^9/L	0.1
Chemistry	Sodium	mmol/L	1
	Potassium	mmol/L	0.1
	chloride	mmol/L	1
	bicarbonate	mmol/L	1
	BUN	mmol/L	0.1
	Glucose	mmol/L	0.1
	Albumin	g/L	0.1
	Creatinine	umol/L	1
	Total bilirubin (direct and indirect)	umol/L	1

Classification	Examination Component	Unit	Rounding Digit
	AST (SGOT)	U/L	1
	ALT (SGPT)	U/L	1
	Alkaline Phosphatase	U/L	1
	Magnesium	mmol/L	0.01
	Phosphorous	mmol/L	0.01
	Calcium	mmol/L	0.01
	Amylase	U/L	1
	Lipase	U/L	1
	Triglycerides	mmol/L	0.01
	Prothrombin time (PT)	seconds	0.1
	Partial Thromboplastin Time (PTT)	seconds	0.1
Thyroid Function Tests	Free T3	pmol/L	0.01
	Free T4	pmol/L	0.1
	Thyroid-stimulating Hormone (TSH)	mIU/L	0.001
Vital Signs	Temperature	degrees	0.1
	Pulse Rate	beats/min	1
	Respiratory rate	breaths/min	1
	Systolic Blood Pressure	mmHg	1
	Diastolic Blood Pressure	mmHg	1
	Height	cm	0.1
	Weight	kg	0.1

3.3.3 Other Safety Assessment Endpoints

Table 6 Electrocardiogram

Classification	Unit	Rounding Digit
Heart Rate	bpm	1
PR	ms	1
QRS	ms	1
RR	ms	1
QTc	ms	1
QTcF	ms	1

4 CASE AND DATA HANDLING

4.1 Case and Data Handling

The criteria listed below will be fulfilled for the handling of each case.

Table 7 Definitions of analysis populations

Analysis Population	Definition
Consented Patients	All Patients who gave informed consent.
Treated Population	This population includes all patients who have received at least 1 dose of study drug. The primary analysis of the primary endpoints and all the secondary endpoints will be performed using the treated population.
Per-protocol (Cytogenetic) Population	This population includes all CP-CML patients in the treated population who have a baseline cytogenetic assessment with at least 20 metaphases examined excluding those with 0/20 Ph+ metaphases at baseline. If at least one treated CP-CML patient does not meet the criteria for per-protocol (cytogenetic) population, a secondary analysis of the primary endpoint will be performed using the per-protocol (cytogenetic) population.
Per-protocol (Hematologic) Population	This population includes all patients in the treated population in AP-CML, BP-CML, and Ph+ ALL Patients who have a baseline BM assessment for which the percentage of BM blasts can be determined, excluding those with MaHR at baseline. If at least one treated AP-CML, BP-CML, or Ph+ ALL patient does not meet the criteria for per-protocol (hematologic) population, a secondary analysis of MaHR will be performed using the per-protocol (hematologic) population.
Dose-Limiting Toxicities (DLT) Evaluable Population (phase I only)	This population includes all patients who complete at least 75% of their planned doses during Cycle 1, unless missed doses are due to AEs**.** This population will be used for DLT assessment and the determination of the maximum tolerated dose.
PK Population	Patients who have at least one PK measurement.

4.2 The Definition of Baseline

The last non-missing valid value collected before and on the date of the first dose of study treatment will be defined as baseline.

4.3 Handling of Missing Values

4.3.1 For Evaluation of CHR/MaHR

For evaluation of CHR/MaHR, missing bone marrow blasts or promyelocytes will be imputed as zero if one of the two values is present.

4.3.2 A Complete Blood Count (CBC) with WBC Differential:

A CBC with WBC differential is required for the determination of MaHR in AP-CML, BP-CML, and Ph+ ALL patients, and Complete Hematologic Response (CHR) in CP-CML

patients. To derive the response status, if the sum of the percentages of the reported cell types of the differential is at least 98%, all other cell types not reported in the differential will be assumed to be 0.

4.3.3 Data Handing for PK Data:

- Concentrations below the limit of quantification, e.g., <0.500
  - Concentrations <0.500 will be imputed as 0 if occurring before T_{max}.
  - Concentration <0.500 will be imputed as 0.25 if occurring right after T_{max}.
  - Subsequent concentrations <0.500 after T_{max} will be imputed as 0.
- Missing data:

  Any observations with missing or time values for PK data will be omitted from the analysis.

- Data after dose adjustment:
  - If a patient had any dose adjustments, including dose interruption and/or reduction, within 7 days of Cycle 2 Day 1 (during Cycle 1 Day 23 to Cycle 2 Day 1), this patient's data will be omitted from the calculations for the dose cohort to which the patient was initially assigned.
  - If a patient in 45 mg cohort had a dose reduction to 30 mg within 7 days of Cycle 2 Day 1 (during Cycle 1 Day 23 to Cycle 2 Day 1), this patient's data will be used for the calculations for 30 mg cohort along with the data from patients in 30 mg cohort. Handling of Efficacy Data.

4.3.4 The Data Handling Rule for Evaluation of MCyR, MaHR, Confirmed MCyR, CHR and MMR:

- For a given visit, if all of the data required to support an assessment of response (see Protocol Appendix A) are not available, the patient will be considered as not a success for that particular visit.

4.3.5 2.The Handling of Missing or Invalid Baseline Values for MCyR:

- Patients with no Ph+ metaphase out of at least 20 metaphase cells at baseline (meeting the criteria for CCyR) will be conservatively analyzed as non-responders in the analysis of the treated population, regardless of whether they maintained response. They will be excluded from the per-protocol (cytogenetic) population.
- Patients with fewer than 20 metaphases examined at baseline will be conservatively analyzed as non-responders in the analysis of the treated population, regardless of post-baseline response. These patients will be excluded from the per-protocol (Cytogenetic)

population. Patients with missing baseline cytogenetic assessments will be analyzed as non-responders.

4.3.6 The Handling of Missing or Invalid Post-baseline Values for MCyR:

At any given cytogenetic assessment, if fewer than 20 metaphases are examined, the determination of PCyR will be based on the handling rules specified in Table 8.

Table 8 Determination of Cytogenetic Response if Examined Metaphases are Fewer Than 20

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.

4.3.7 The Handling Rule for Baseline MaHR Status:

Eligibility criteria require that AP-CML, BP-CML, and Ph+ ALL patients not enter the trial already in MaHR. Two of the three assessments required for the determination of MaHR, CBC with differential and a physical examination (including assessment of extra-medullary disease) are performed at screening and on Cycle 1 Day 1. The last valid assessment will be used as the baseline assessment.

4.3.8 The Data Handling Rule for MaHR:

- Patients, who meet the criteria for MaHR at baseline, will be conservatively analyzed as non-responders for the analysis of the treated population and will be excluded from the per-protocol (hematologic) population.
- Patients, for whom bone marrow blasts are not determined at baseline, will be conservatively analyzed as non-responders in the analysis of the treated population, regardless of post-baseline response. These patients will be excluded from the per-protocol (hematologic) population.
- A bone marrow aspirate is required for a patient to be considered as meeting the criteria for MaHR. Missing bone marrow blasts or promyelocytes will be imputed as zero if one of the two values is present. (This rule is also described in "4.3 Handling of

missing values".) MaHR will be confirmed by a peripheral blood CBC and differential no earlier than 28 days after the initial assessment of MaHR.

- The assessments for bone marrow aspirate, CBC with differential, and physical examination need be performed within 14 days of one another to assess whether a patient meets the criteria for MaHR or not. 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 will be confirmed by a peripheral blood CBC and differential no earlier than 28 days later.

4.4 Handling of Safety Data

4.4.1 Handling of Adverse Events

Treatment-emergent AEs are the AEs that start on or after the first dose date and the AEs whose partially available start date cannot rule out the possibility of starting on or after the first dose date.

All AEs reported in the database during the on-study period will be included in the listing of AEs and each AE will be flagged as treatment-emergent or not.

Treatment-Emergent Adverse Event Flag

- Sites may "split" AEs that are ongoing as of first dose date into two records: one that ends as of first dose date and one that begins on first dose date. Therefore in some cases, what may at first appear as an AE that begins on first dose date is really a continuation of an AE that began prior to first dose date. If all of the following criteria are met for any two AE records then the two records should be considered as one event for purposes of assessing a treatment-emergent adverse event, as they were present prior to treatment and did not worsen in severity or relatedness:
  - The preferred term of the first AE = the preferred term of the second AE.
  - The start date of the first AE is before the date of first dose.
  - The end date of the first AE is one day before the date of first dose or equal to the date of first dose.
  - The start date of the second AE = the date of first dose.
  - The severity of the second AE ≤ the severity of the first AE.
  - The relatedness of both the first and the second AEs is "Not Related".
- After determining which records should be treated as a single event, the treatment-emergent flag can be determined as follows:
  - All AEs with an onset date on or after the first dose date and no later than 30 days after the last dose date.

- In the case of missing onset date, impute using the rules defined in the following Section 3 then determine if imputed date is on or after first dose date.

Treatment-Related Adverse Event Flag

- All AEs for which relationship to study treatment is classified as "Possibly Related", "Probably Related", or "Definitely Related"
- If relationship to study treatment is missing, then the relationship will be imputed as treatment related.
- Imputations are for the purposes of aggregated summaries of AEs. Listings of individual AEs should not display the imputed relationship.

Imputation Rules for Missing Onset and Resolution Date

In general the imputation should be conservative, such that onset dates should be imputed to be as early as possible and resolution dates will be imputed to be as late as possible. Impute resolution date first and then impute onset date using imputed resolution date.

Resolution Date

- If day is missing but month and year are non-missing (YYYY-MM-UU), impute as the earliest of:
  - Last day of the month (28, 29, 30, or 31, depending on in which month the adverse event resolved)
  - Last contact date for patients who did not start follow-up or discontinued follow-up due to a reason other than death
  - Data cut-off date
  - Death date
- If day and month are missing (YYYY-UU-UU), impute as the earliest of:
  - December 31 (YYYY-12-31)
  - Last contact date for patients who did not start follow-up or discontinued follow-up due to a reason other than death
  - Data cut-off date
  - Death date
- If date is completely missing (i.e. AE is ongoing):
  - For AEs meeting the criteria for seriousness or of special interest, impute as earliest of:
    - Data cut-off date
    - Death date

- For the other AEs, impute as earliest of:
  - Data cut-off date
  - Last contact date for patients who did not start follow-up or discontinued follow-up due to a reason other than death
  - Treatment discontinuation date + 30 days
  - Death date

Onset Date

If day is missing but month and year are non-missing (YYYY-MM-UU), impute as follows:

- If year and month are the same as year and month of first dose date:
  - If resolution date (or imputed resolution date) is on or after first dose date, impute as first dose date.
  - If resolution date (or imputed resolution date) is prior to first dose date, impute as latest of:
    - First day of month
    - Informed consent date
- If year is the same as year of first dose date and month is after month of first dose date, impute as first date of month.
- If year is the same as year of first dose date and month is before month of first dose date, impute as latest of:
  - First day of month
  - Informed consent date
- If year is after year of first dose date, impute as first day of month.
- If year is before year of first dose date, impute as latest of:
  - First day of month
  - Informed consent date

If day and month are missing and year is non-missing (UU-UUU-YYYY), impute as follows:

- If year is the same as year of first dose date:
  - If resolution date (or imputed resolution date) is on or after first dose date, impute as first dose date.
  - If resolution date (or imputed resolution date) is prior to first dose date, impute as latest of:
    - First day of month
    - Informed consent date
- If year is after year of first dose date, impute as January 1 (YYYY-01-01).

- If year is before year of first dose date, impute as latest of:
  - January 1 (YYYY-01-01)
  - Informed consent date

If date is completely missing:

- If resolution date (or imputed resolution date) is on or after first dose date, impute as first dose date.
- If resolution date (or imputed resolution date) is prior to first dose date, impute as informed consent date.

Some preferred terms coding manifestations of similar medical conditions will be re-grouped based on the synonym infrastructure determined through sponsor medical review.

4.4.2 Handling of Other Safety Data

Data that meet any of the criteria below will be treated as missing, and excluded from all analyses.

Treated as missing due to reference value	If measurements other than PK data are considered inappropriate because hemolysis, fibrin or other abnormalities are found in the sample, they are treated as missing values. Additionally, if units and/or reference ranges for measurements are missing, the measurements are treated as missing values.

4.5 Handling of Longitudinal Data

4.5.1 Calculation Method of Number of Days

Number of days is calculated by the following formula:

- Number of Days (n) = Day of event First Day of event + 1

Therefore, the first day of event will be Day 1, and the next day will be Day 2.

Duration is calculated using number of days as follows:

- Year: number of days/365.25
- Month: number of days/(365.25/12)

4.5.2 Time Windows

Calculation of summary statistics over time is done by each CRF visit and even if actual visit date is deviated from the planned data, all the data will be included in the analysis without considering time window, unless otherwise specified.

5 STATISTICAL ANALYSIS

5.1 Significance Level, Confidence Interval

No formal statistical hypothesis testing will be done for the primary endpoints. The primary analysis of the primary endpoints and secondary efficacy endpoints will be performed using an exact 1-sided 95% lower confidence limit. For the primary endpoints and secondary efficacy endpoints, the 2-sided 95% confidence interval (CI) will be provided as well. For all the other parameters to be estimated, the 2-sided 95% confidence interval will be provided.

5.2 Multiplicity

No adjustment will be made for multiplicity in this study.

5.3 Analysis Methods

5.3.1 Descriptive Statistics

Descriptive statistics defined in this SAP include the number of subjects (N), arithmetic mean, standard deviation, minimum, median, and maximum of the data, if not specified.

5.3.2 Incidence Rates of Treatment-Emergent Adverse Events/Drug Related Adverse Events

The incidence rates of TEAEs or drug related AEs are calculated as a percentage of the number of subjects with AEs or drug related AEs in Treated Population:

$$\text{Incidence Rate}\,(\%) = \frac{\text{The Number of P}\textit{atient}\text{s with TEAEs/Drug Related AEs}}{\text{Treated Population}} \times 100$$

5.4 Rounding Digits

5.4.1 Displaying of Descriptive Statistics

Arithmetic Mean, Standard Deviation, and Median

- Rounded to one more significant digit than what was used to collect the variable.

Minimum and Maximum

- Rounded to the same number of significant digits used to collect the variable.

If multiple significant digits are measured among subjects, set an alternative significant digit.

5.4.2 Rounding Digits for Percentages

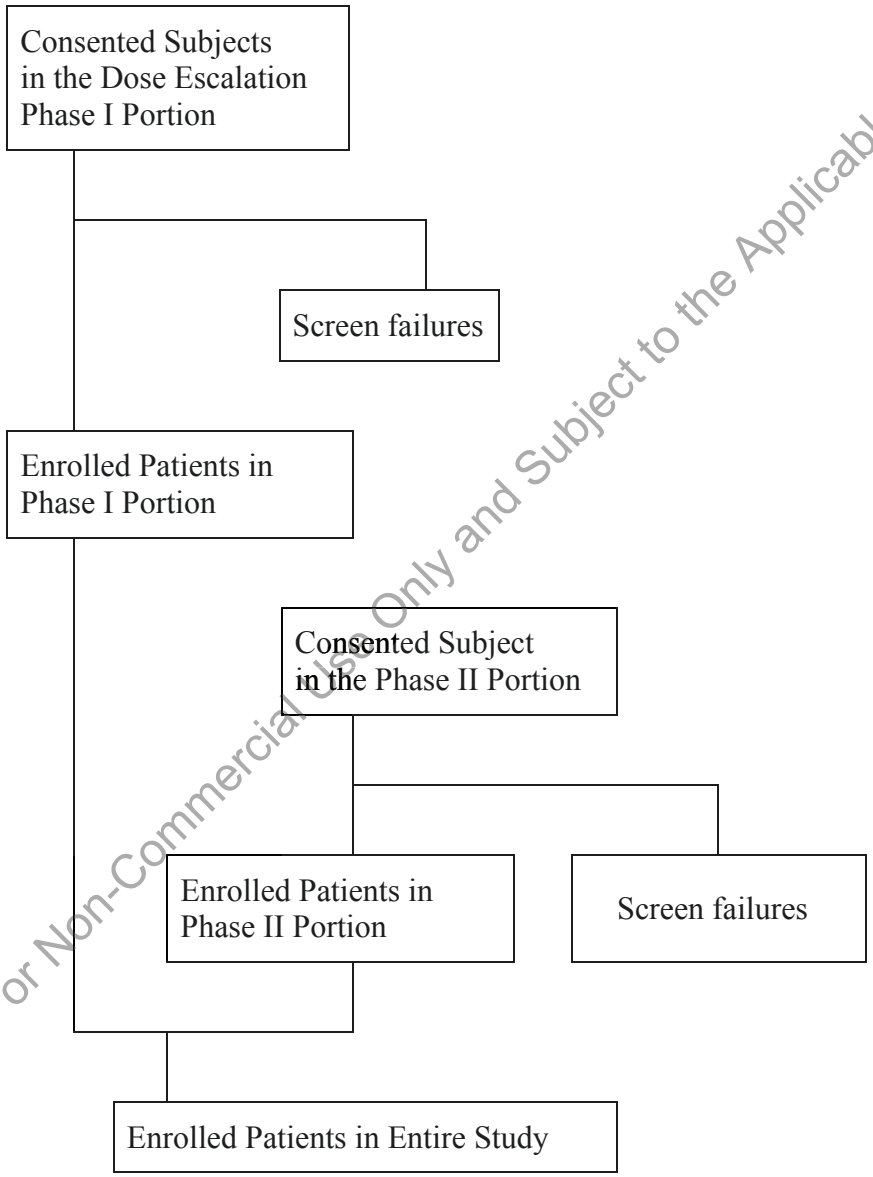
Round to the nearest tenths (0.1).

6 SUBJECT DISPOSITION

6.1 Flowchart of Subject Disposition

Population: Consented Patients

Contents: Calculate the number of following Patients:



6.2 Subject Disposition

Population: Treated Patients

Contents: Disposition tables by phase/dose and by diagnosis are created:

- Calculate the patient number in Treated Population.
- Calculate the patient number and percentage of DLT Evaluable Population.
- Calculate the number and percentage of patients who discontinued treatment and primary reason of treatment discontinuation.
- Calculate the patient number and percentage of patients who discontinued study and the primary reason for study discontinuation.
- Calculate the patient number and percentage of patients who died on study and by death reason.
- Calculate the summary statistics of duration of follow-up.
- These numbers of patients or percentages above are calculated for the patient groups defined in Table 3 Definition of Patient Groups.

7 STUDY POPULATIONS, DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS, AND STUDY DRUG ADMINISTRATION

7.1 Demographics and Other Baseline Characteristics

Population: Treated Population

Contents: Examine the distribution of demographics and other baseline characteristics.

For categorical data and ordinal data, calculate the number of subjects and percentages. For continuous data, calculate the descriptive statistics.

Summarize Demographics and Other Baseline Characteristics by the patient groups defined in Table 3 Definition of Patient Groups.

Definitions: **Age**: Age at the time of informed consent.

BMI: BMI will be calculated by dividing weight (kg) by square of height (m).

Unknown and Missing values: If unknown or missing values are observed, add "Unknown" category and only calculate the number of subjects. Remove "Unknown" category from the denominator for incidence rates and from tests.

Classification [Unit]	Category/Statistics
Gender	Male, Female
Age [Year]	N, Mean, Standard Deviation, Minimum, Median, Maximum
	Between 18 and 44 , Between 45 and 64, At least 65 (≥65)
	< 50, 50 - 65, 65 < - <75, ≥ 75
Race	Asian
Diagnosis	CP-CML, AP-CML, BP-CML, Ph+ ALL
Years since initial diagnosis of current phase	N, Mean, Standard Deviation, Minimum, Median, Maximum
	<5, 5-<10, ≥10
Major Cytogenetic response Status	CCyR, PCyR, Less than PCyR, Less than 20 metaphases examined, missing

Classification [Unit]	Category/Statistics
Major Hematologic response Status	Valid bone marrow blasts, not in MaHR Valid bone marrow blasts, in MaHR Bone marrow blasts not determined
Complete Hematologic response Status (CP-CML patients)	Not in CHR CHR
CCI	
CCI	
Prior Exposure to Dasatinib and Nilotinib	Dasatinib, Nilotinib, Dasatinib and Nilotinib, Dasatinib or Nilotinib
Reason for Stopping the Last Dasatinib	Resistant, Intolerant, Other
Reason for Stopping the Last Nilotinib	Resistant, Intolerant, Other
Prior exposure to TKI(s)	Imatinib Dasatinib Nilotinib Bosutinib Bafetinib (INNO-406) KW-2449 Tozasertib (NK – 0457) Danusertin (PHA-739358) XL228 DCC-2036 Radotinib
Prior exposure to TKI(s) (Number of TKIs)	N, Mean, Standard Deviation, Minimum, Median, Maximum
	0, 1, 2, ≥3, Missing
Prior exposure to Approved TKI(s)	1 Approved TKI IMATINIB only DASATINIB only NILOTINIB only 2 Approved TKIs IMATINIB + DASATINIB IMATINIB + NILOTINIB DASAT INIB+ NILOTINIB 3 Approved TKIs IMATIB + DASATINIB + NILOTINIB
Number of prior regimens	1, 2, 3, 4, 5, 6, >6

Classification [Unit]	Category/Statistics
Resistance/Intolerance	Resistant to Dasatinib or Nilotinib Resistance to Dasatinib/Nilotinib Only Both resistant & Intolerant to Dasatinib/Nilotinib Intolerant to Dasatinib/Nilotinib Only Neither resistant nor Intolerant to Dasatinib/Nilotinib
Best response to most recent Dasatinib or Nilotinib containing regimen	CMR MMR CCyR PCyR Less than PCyR MaHR (AP-CML, BP-CML, Ph+ ALL) CHR (CP-CML) Stable None/Progressive disease Unknown
Best response to most recent anti-leukemia regimen	CMR MMR CCyR PCyR Less than PCyR MaHR (AP-CML, BP-CML, Ph+ ALL) CHR (CP-CML) Stable None/Progressive disease Unknown
BCR/ABL/ABL ratio (IS)	≤ 0.0032% 0.0032% - ≤ 0.01% 0.01% - ≤ 0.1% 0.1% - <- 1% 1% - ≤10% >10% E1a2 variant Atypical Transcripts Missing
Prior Stem Cell Transplant	Yes, No
Prior Exposure to Homoharringtonine	Yes, No
Prior Chemotherapy	Yes, No
Reason for Stopping the Last Cancer Therapy.	Resistant, Intolerant, Other
Extramedullary Involvement (location)	Splenomegaly, hepatomegaly, Other, No extramedullry involvement, Missing
ECOG Performance Status	Not Assessed, Grade 0, Grade 1, Grade 2, Grade 3, Grade 4, Grade 5
Weight [kg]	N, Mean, Standard Deviation, Minimum, Median, Maximum

Classification [Unit]	Category/Statistics
Height [kg]	N, Mean, Standard Deviation, Minimum, Median, Maximum
BMI[kg/m^2]	N, Mean, Standard Deviation, Minimum, Median, Maximum

7.2 Drug Study Administration

Population: Treated Population

Contents: Calculate descriptive statistics of the following variables:

- Treatment period
- Number of days dosed
- Actual Total dose
- Dose intensity
- Relative Dose intensity

Calculate the following subject number and percentage:

- Subjects whose Dose was reduced
- Subjects whose Dose was interrupted for at least 3 days

Patient groups are defined in Table 3 Definition of Patient Groups.

Definitions: **Planned Total dose (mg)**: treatment period for each dosage

Actual Total dose (mg): Sum of actual dosages taken (if dosage changed, actual total dose will be calculated by each dose)

Relative Dose Intensity (%): (Actual Total dose/Planned Total dose)*100(%)

Treatment period (days): Last day of study drug administration (or Date of withdrawal) - First day of Test Drug administration+1

Dose Intensity (mg/day):(Actual Total dose/ Treatment period)

The last day of Cycle 1: defined as 28 days after the first dosing day (the day=the first administration day+27)

8 EFFICACY ASSESSMENT

8.1 Primary Endpoints

8.1.1 Primary Analysis of Primary Endpoints

Population: Treated Population

Contents: **<CP-CML Patients>**

Primary Endpoint: MCyR

The primary analysis of the primary efficacy endpoint of MCyR is performed by calculating MCyR rate and its exact 1-sided 95% lower confidence limit using the all CP-CML patients treated in the phase I portion and phase II portion.

Proportion of each category included in MCyR (CCyR, PCyR) will also be presented.

<AP-CML, BP-CML, Ph+ ALL Patients>

Primary Endpoint: MaHR

The primary analysis of the primary efficacy endpoint of MaHR will be performed by calculating MaHR and its exact 1-sided 95% lower confidence limit using the all AP-CML, BP-CML, and Ph+ ALL patients treated in the phase I portion and phase II portion for combined data across these disease groups.

Additionally, same analysis is done by the following group:

- AP-CML
- BP-CML
- Ph+ ALL

Proportion of each category included in MaHR (CHR, NEL) will also be presented.

Definitions: **<CP-CML Patients>**

Primary Endpoint: MCyR

Major cytogenetic response rate: The proportion of patients who have achieved a CCyR (no Ph+ cells) or PCyR (1-35% Ph+ cells) by 12 months after the initiation of study treatment. Patients entering the study already in PCyR must achieve a CCyR by 12 months in order to be considered a success for the MCyR rate.

<AP-CML, BP-CML, Ph+ ALL Patients>

Primary Endpoint: MaHR

Major hematologic response rate: The proportion of patients who have achieved a confirmed CHR or NEL by 6 months after the initiation of study treatment.

The primary analysis of the primary endpoints and secondary endpoints will be performed after the last enrolled patient has completed the 12th 28-day cycles of treatment using all data collected at that time.

8.1.2 Sensitivity Analysis of Primary Endpoints

Population: Treated Population

Contents: **<CP-CML Patients>**

The sensitivity analysis of MCyR for CP-CML patients will be performed by calculating MCyR rate at or by 3-month assessment, 6-month assessment, 9-month assessment, 12-month assessment, and during the entire on study treatment period after the initiation of study treatment using the treated population, i.e., CP-CML patients treated in the phase I portion and phase II portion.

Proportions of patients who have achieved CCyR and PCyR will also be presented.

<AP-CML, BP-CML, Ph+ ALL Patients>

The sensitivity analysis of MaHR will be performed by calculating MaHR during the entire on study treatment period and its exact 1-sided 95% lower confidence limit using the treated population, i.e., total patients treated in the phase I portion and phase II portion for each individual disease group and the combined disease group (AP-CML, BP-CML, and Ph+ ALL).

Proportions of patients who have achieved CHR and NEL will also be presented.

8.1.3 Additional Analysis of Primary Endpoints

Additional analysis of the primary endpoints may be performed using the per-protocol populations if any treated patients do not meet the criteria for per-protocol populations.

Population: Per-protocol Population

Contents: **<CP-CML Patients>**

Additional analysis of MCyR for CP-CML patients may be performed by calculating MCyR rate by 12 months and its lower 1-sided exact 95% limit using the per-protocol (cytogenetic) population, i.e., CP-CML patients treated in the phase I portion and phase II portion and had a baseline cytogenetic assessment with at least 20 metaphases examined and no CCyR at baseline.

Proportions of patients who have achieved CCyR and PCyR will also be presented.

<AP-CML, BP-CML, Ph+ ALL Patients>

Additional analysis of MaHR may be performed by calculating MaHR by 6 months and its exact 1-sided 95% lower confidence limit for MaHR rate using the per-protocol (hematologic) population, i.e., total patients enrolled in the phase I portion and the phase II portion for each individual disease group and the combined disease group (AP-CML, BP-CML, and Ph+ ALL) excluding those with MaHR at baseline.

Proportions of patients who have achieved CHR and NEL will also be presented.

8.1.4 Bayesian Analysis

Population: Treated population in this trial and per-protocol Population in study AP24534-10-201 (PACE)

Contents: Bayesian inference of the response rates is carried out under the following assumptions: 1. The number of patients who achieved the primary endpoint in the study populations of this study and PACE study follows a binomial distribution, binominal(p, n); 2. P has a prior distribution beta(a, b). The posterior distribution of p given that y patients achieve the primary endpoint is beta(n+a, n-y+b). Bayesian analysis is implemented using PROC MCMC in SAS. The estimated 1-sided 95% lower credible limit and 1-sided 95% lower highest posterior density limit of the observed response rates are presented.

For CP-CML, MCyR rate by 12 months is analyzed.

For AP-CML, BP-CML, and Ph+ ALL Patients, Confirmed MaHR rate by 6 months is analyzed for each disease group and the combined disease group.

Definitions: **MCyR**: Same as the Definition of 8.1 Primary Analysis of Primary Endpoint.

MaHR: Same as the Definition of 8.1 Primary Analysis of Primary Endpoint.

8.2 Secondary Endpoints

8.2.1 Confirmed MCyR (cCCyR or cPCyR)

Population: Treated Population

Contents: The analysis will be performed by calculating confirmed MCyR rate and an exact 1-sided 95% lower confidence limit using the treated population. Proportions of patients who have achieved cCCyR and cPCyR will also be presented. Confirmed MCyR rate will be evaluated for the patient groups defined in Table 3.

Definitions **Confirmed MCyR:** The proportion of patients who have achieved a confirmed CCyR or PCyR at least 28 days apart after the initiation of study treatment. Patients entering the study already in PCyR must achieve a confirmed CCyR at least 28 days apart in order to be considered as a success for the confirmed MCyR rate.

8.2.2 Confirmed CHR

Population: Treated Population in CP-CML

Contents: The analysis will be performed by calculating confirmed CHR rate and the exact 1-sided 95% lower confidence limit using the treated population in CP-CML patients.

Definitions: **Confirmed CHR**: The proportion of patients who have achieved a confirmed CHR at least 28 days apart after the initiation of study treatment.

8.2.3 Major Molecular Response

Analysis of Molecular Response

Population: Treated Population

Contents: The analysis will be performed by calculating Major molecular response (MMR) rate during the entire on study treatment time interval after the initiation of study treatment and the exact 1-sided 95% lower confidence limit using the treated population.

Analysis will be done for patient groups defined in Table 3.

Definitions: CCI [redacted]

Additional Analysis of Molecular Response

Population: Treated Population

Contents: The analysis will be performed by calculating the rates of MR4, MR4.5, MR5 at or by 3-month assessment, 6-month assessment, 9-month assessment, 12-month assessment, and during the entire on study treatment interval after the initiation of study treatment.

Analysis will be performed for the patient groups defined in Table 3.

Definitions: CCI [redacted]

Duration of Response

Population: Treated Population

Contents: Duration of response is estimated using the Kaplan-Meier method.

The following number of patients and statistics will be presented:

- Number of Patients evaluated
- Number of Patients with Events and its percentage
- Number of Patients censored and its percentage
- Minimum duration
- 25th Percentile Duration
- Median Duration
- The exact 1-sided 95% lower confidence limit of Median Duration
- The 2-sided 95% CI of Median Duration
- 75th Percentile Duration
- Maximum Duration
- Probability of not losing the response after 6 months
- The 2-sided 95% CI of Probability of not losing the response after 6 months
- Probability of not losing the response after 12 months
- The 2-sided 95% CI of Probability of not losing the response after 12 months

For CP-CML, MCyR, CHR and MMR will be evaluated.

For AP-CML, BP-CML and Ph+ ALL, confirmed MaHR, MCyR, MMR will be evaluated.

Population: Treated Population

Definitions **Duration of response**: the interval between the first assessment at which the criteria for response are met until the criteria for loss of response are met, censored at the last valid response assessment date. If a patient has had one response assessment at which the response criteria are met and no further evaluable response assessments, the duration of response will be 1 day. Duration of response is defined for patients who have achieved the primary endpoints, i.e., CP-CML patients who achieved MCyR by 12 month and AP-CML/BP-CML/Ph+ ALL patients who achieved MaHR by 6 month. Duration of CHR or MMR is defined for patients who have achieved response during the entire on study treatment period.

Loss of MCyR: 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 or multiple 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 or CCyR. Patients with a single or multiple cytogenetic assessments with Ph+ > 35% followed by no additional cytogenetic assessments will also be considered as meeting the criteria for loss of MCyR.

Loss of MaHR: 2 consecutive hematologic assessments ≥ 28 days apart at which the criteria for MaHR are not met. Patients with a single or multiple hematologic assessments at which the criteria for MaHR are not met followed by no additional hematologic assessments will also be considered as meeting the criteria for loss of MaHR.

Loss of CHR: 2 consecutive hematologic assessments ≥ 28 days apart at which the criteria for CHR are not met. Patients with a single or multiple hematologic assessments at which the criteria for CHR are not met followed by no additional hematologic assessments will also be considered as meeting the criteria for loss of CHR.

Loss of MMR: 2 consecutive molecular assessments ≥ 28 days apart at which the criteria for MMR are not met. Patients with a single or multiple molecular assessments at which the criteria for MMR are not met followed by no additional molecular assessments will be also considered as meeting the criteria for loss of MMR.

8.2.4 Progression-Free Survival

Population: Treated Population

Contents: Progression-free survival is estimated using the Kaplan-Meier method.

The following number of patients and statistics will be presented:

- Number of Patients evaluated
- Number of Patients with Events and its percentage
- Number of Patients censored and its percentage
- Minimum PFS
- 25th Percentile PFS
- Median PFS
- The exact 1-sided 95% lower confidence limit of Median PFS
- The 2-sided 95% CI of Median PFS
- 75th Percentile PFS
- Maximum PFS
- Probability of Progression-free after 6 months
- The 2-sided 95% CI of Probability of Progression-free after 6 months
- Probability of Progression-free after 12 months
- The 2-sided 95% CI of Probability of Progression-free after 12 months

Population: Treated Population

Evaluated by the following groups:

- CP-CML
- Pooled group (AP-CML, BP-CML and Ph+ ALL)

Definitions: **Progression-free survival**: the interval from the first dose of study treatment until the criteria for progression are met or death, censored at the last response assessment.

The criteria for progression and date of disease progression are specified as follows,

In CP-CML patients, disease progression date is defined as the earliest of the following dates:

- Death date
- Last dose date of patients who discontinued study treatment due to disease progression.
- Initial date of the loss of MMR which is subsequently confirmed or the date of single loss followed by no additional assessment.
- Initial date of the loss of MCyR, which is subsequently confirmed or the date of single loss followed by no additional assessment.
- Initial date of the loss of CHR after the confirmation of CHR if patients have not achieved MCyR. Loss of CHR should be subsequently confirmed or followed by no additional assessment.
- Initial date of developing AP/BP (as defined in Table 1 in the protocol) based on the evaluation of peripheral blood and bone marrow at least 28 days after the first dose date, and after the dates of CHR confirmation, first MCyR and first MMR if patients have achieved any response(s).
- Initial date of doubling of WBC to greater than 20,000 x109/L on 2 occasions at least 4 weeks apart, at least 28 days after the first dose date, and after the dates of CHR confirmation, first MCyR and first MMR if patients have achieved any response(s).

In AP-CML patients, disease progression date is defined as the earliest of the following dates:

- Death date
- Last dose date of patients who discontinued study treatment due to disease progression.
- Initial date of the loss of MaHR after the confirmation of MaHR if patients have two instances of loss of MaHR at least 14 days apart
- Initial date of increased peripheral blast or bone marrow blast to at least 30%, at least 28 days after the first dose date, and after the dates of MaHR confirmation, first MCyR and first MMR if patients have achieved any response(s).
- Initial date of the same as or worsening blast count from baseline at least 28 days after the first dose date, and after the dates of MaHR confirmation, first MCyR and first MMR if patients have achieved any response(s), in the following situations: post-baseline peripheral blasts are equal to or greater than baseline peripheral blasts when baseline peripheral blasts are non-missing; post-baseline peripheral blasts greater than 0 when baseline peripheral blasts are missing; post-baseline bone marrow blasts are greater than 5% and are equal to or greater than baseline bone marrow blasts when baseline bone marrow blasts are non-missing; post-baseline bone marrow blasts are greater than 5% when baseline bone marrow blasts are missing.

In BP-CML and PH+ ALL patients, disease progression date is defined as the earliest of the following dates:

- Death date
- Last dose date of patients who discontinued study treatment due to disease progression.
- Initial date of the loss of MaHR after the confirmation of CHR if patients have two instances of loss of MaHR at least 14 days apart
- Initial date of the same or worsening blast from baseline at least 28 days after the first dose date, and after the dates of CHR confirmation, first MCyR and first MMR if patients have achieved any response(s), in the following situations: post-baseline peripheral blasts are greater than baseline peripheral blasts when baseline peripheral blasts are non-missing; post-baseline peripheral blasts are greater than 0 when baseline peripheral blasts are

Population: Treated Population

missing; post-baseline bone marrow blasts are greater than 5% and are greater than baseline bone marrow blasts when baseline bone marrow blasts are non-missing; post-baseline bone marrow blasts are greater than 5% when baseline bone marrow blasts are missing.

8.2.5 Overall Survival

Population: Treated Population

Contents: Overall survival is estimated using the Kaplan-Meier method.

The following number of patients and statistics will be presented:

- Number of Patients evaluated
- Number of Patients with Events and its percentage
- Number of Patients censored and its percentage
- Minimum OS
- 25th Percentile OS
- Median OS
- The exact 1-sided 95% lower confidence limit of Median OS
- The 2-sided 95% CI of Median OS
- 75th Percentile OS
- Maximum OS
- Probability of Survival after 6 months
- The 2-sided 95% CI of Probability of Survival after 6 months
- Probability of Survival after 12 months
- The 2-sided 95% CI of Probability of Survival after 12 months

Evaluated by the following groups:

- CP-CML
- Pooled group (AP-CML, BP-CML and Ph+ ALL)

Definitions **Overall Survival**: 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.

8.2.6 Time to Response

Population: Treated Population

Contents: Time to response is estimated using the Kaplan-Meier method. Time to response will also be summarized with descriptive statistics for responders only.

The following number of patients and statistics will be presented:

- Number of Patients evaluated
- Number of Patients with Events and its percentage
- Number of Patients censored and its percentage
- Minimum time to response
- 25th Percentile time to response
- Median time to response
- The exact 1-sided 95% lower confidence limit of Median time to response
- The 2-sided 95% CI of Median time to response
- 75th Percentile time to response
- Maximum time to response

Population: Treated Population

- Probability of observing the response until 6 months
- The 2-sided 95% CI of Probability of observing the response until 6 months
- Probability of observing the response until 12 months
- The 2-sided 95% CI of Probability of observing the response until 12 months

For CP-CML, MCyR, time to CHR and MMR will be evaluated.

For AP-CML, BP-CML and Ph+ ALL, time to MaHR, MCyR, and MMR will be evaluated.

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

8.3 Covariate Adjustments

N/A

8.4 Multicenter Study

Evaluation by each site is not done.

8.5 8.5 Subgroup Analysis

Subgroup analysis of the primary endpoint and selected secondary endpoints will be performed in patients formed according to time since initial diagnosis of current phase, mutation at baseline, and prior approved TKI therapies.

- Patient groups based on time since initial diagnosis of current phase
  - 0 - ≤ first tertile
  - first tertile - ≤ second tertile
  - second tertile
- Patient groups based on mutation at baseline
  - T315I
    - T315I only
    - T315I + 1 additional mutation
  - Other
    - One mutation other than T315I
    - No mutation
    - No sequencing data
- Patient groups based on prior approved TKI(s)
  - 1 approved TKI
    - Any
    - Dasatinib
    - Nilotinib

- 2 approved TKIs
  - Any
  - Imatinib + Dasatinib
  - Imatinib + Nilotinib
  - Dasatinib + Nilotinib
- 3 approved TKIs
  - Imatinib + Dasatinib + Nilotinib

8.6 Stratified Analysis

N/A

8.7 Interim Analysis

No formal interim analyses are planned for efficacy in this study.

9 PK ASSESSMENT

9.1 PK Analysis

9.1.1 Ponatinib Concentration at Each Time Point

Population: PK Population

Contents: Calculate descriptive statistics (Arithmetic mean, SD, Minimum, Median, Maximum, 95% confidence intervals, Geometric mean and CV% (coefficient of variation)) of ponatinib concentration in each time point by each dose level (15 mg, 30 mg and 45 mg)

Mean of concentration at each time point will be plot with an error bars (SD).

9.1.2 PK Parameters Estimated from PK Profile

Population: PK Population

Contents: Calculate the descriptive statistics (Arithmetic mean, SD, Minimum, Median, Maximum, 95% confidence intervals, Geometric mean and CV% (coefficient of variation)) for the following PK parameters by Dose level (15 mg, 30 mg and 45 mg) and at each time point:

- Cmax [ng/mL]
- AUC(0-24h) [hr*ng/mL]
- Tmax [hr]
- Elimination half-life (t1/2)[hr]
- CLss/F
- Vd/F
- RA(AUC)

Definitions: **C_{max} [ng/mL]** :Observed maximum concentration

$AUC_{(0\text{-}24h)}$[hr*ng/mL] :Area under the observed concentration- time curve from $AUC_{(0\text{-}24h)}$ calculated using linear trapezoidal method.

T_{max} [hr] :Time point of C_{max}

Elimination half-life ($t_{1/2}$) [hr] :Calculated as –In(2)/(Elimination rate constant for terminal phase). Elimination rate constant for terminal phase is derived from the log-linear regression

Population: PK Population

on the terminal phase with several measurements.

CLss/F: the apparent clearance at steady-state, unadjusted for bioavailability that is calculated as Dose/AUC $_{(0\text{-}24h)}$.

Vd/F: the apparent volume of distribution, unadjusted for bioavailability that is calculated as CLss/F * (Elimination rate constant for terminal phase).

$R_{A(AUC)}$: AUC $_{0\text{-}24h\ Cycle\ 2\ Day\ 1}$/ AUC $_{0\text{-}24h\ Cycle\ 1\ Day\ 1}$

(For 15 mg, AUC $_{0\text{-}24h\ Cycle\ 1\ Day\ 8}$/ AUC $_{0\text{-}24h\ Cycle\ 1\ Day\ 1}$)

9.1.3 Dose-Linearity Among Dose Levels

Population: PK Population

Contents: Evaluate Dose-linearity among dose levels (15 mg, 30 mg and 45 mg) using power model in terms of C_{max} and $AUC_{(0\text{-}24h)}$ at Cycle 1 Day 1 and Cycle 2 Day 1(For 15 mg, Cycle 1 Day 1 and Cycle 1 Day 8).

CCI [redacted]

9.1.4 Comparison Between this Study and Study Conducted in US(USA101).

Population: PK Population

Contents: Comparison is based on dose-normalized mean of logarithmically-transformed C_{max} and $AUC_{(0\text{-}24h)}$. No formal hypothesis testing is planned. At each dose level (30 mg and 45 mg) and for pooled group (30 mg and 45 mg), the PK parameters and the descriptive statistics for both studies will be displayed side-by-side.

9.1.5 Box and whisker plots of the steady-state, dose-normalized $AUC_{(0\text{-}24h)}$ and C_{max}

Population: PK Population

Contents: Box and whisker plots of the steady-state, dose-normalized $AUC_{(0\text{-}24h)}$ and C_{max} will be created for data of this trial and US trial (AP24534-07-101).

Dose-normalized $AUC_{(0\text{-}24h)}$ and C_{max} will be plotted by each dose (30 mg and 45 mg)

9.1.6 PK Listings

Listing of Ponatinib Concentration

Listing of Pharmacokinetic parameters

10 SAFETY ASSESSMENT

10.1 Treatment-Emergent Adverse Events/ Drug Related Adverse Events

10.1.1 Numbers and Incidence Rate of Patients with Treatment-emergent Adverse Events

Population: Treated Population

Contents: Calculate the subject number for the followings:

- Number of Patients
- Number of Patients with TEAE
- Number of Patients with Grade 3/4/5 TEAE
- Number of Patients with Serious TEAE
- Number of Patients with TRAE
- Number of Patients with Grade 3/4/5 TEAE
- Number of Patients with Serious TRAE
- Number of Patients with TEAE Leading to Treatment Discontinuation, Reduction, Interruption, or Study Discontinuation

Calculate the number of subjects by the following groups:

- 30 mg
- 15/45 mg
- Total

10.1.2 Numbers and Incidence Rate of Patients with Treatment-emergent Adverse Events by MedDRA Code

Population: Treated Population

Contents: Calculate the number of subjects with TEAEs, incidence rates and percentages, by System Organ Class (SOC) and Preferred Term (PT) for the patient groups defined in Table 1.

- Denominator to calculate the percentage: The number of subjects from the population in each group.
- Each subject with more than one AE will be counted once (a subject with one or more AEs will only be counted once).

Conduct the same analysis for Drug Related AEs, Serious AEs and Serious drug related AEs.

10.1.3 Numbers and Incidence Rate of Patients with Treatment-Emergent Adverse Events According to Severity by MedDRA Code

Population: Treated Population

Contents: Calculate the number of subjects with AEs, incidence rates and percentages, by SOC and PT and CTCAE grade for the following patient groups initially treated at 30 mg, 15/45 mg, and any dosage:

- CP-CML
- Pooled group for advanced phases (AP-CML, BP-CML, and Ph+ ALL)

Denominator to calculate the percentage: The number of subjects from the population in each group.

Each subject with more than one AE will be counted once at the greatest CTCAE grade (a

Population: Treated Population

subject with one or more AEs will only be counted once).

Conduct the same analysis for d related AEs, Serious AEs and Serious related AEs.

10.2 Assessments of Laboratory Test Results, Vital Signs, Left Ventricular Ejection Fraction, and QTcF Interval

10.2.1 Descriptive Statistics of Transition of Laboratory Test (Haematology) Results

Population: Treated Population

Contents: Calculate summary statistics for the baseline, the lowest post-baseline level and the highest post-baseline level.

Calculate the patient numbers and percentages by shift in CTCAE grade from the baseline to the worst on-study result as follows:

- No change from baseline,
- Any worsening from baseline
- Worsening to grade 3 or grade 4
- <Grade 3 to grade 3
- <Grade 3 to grade 4
- Worsening to <grade 3
- Improved from baseline
- Unable to evaluate (note: missing at baseline or post-baseline)

Definitions: **ANC**: White Blood Cell Counts* Neutrophil percentage (%)

10.2.2 Descriptive Statistics of Transition of Laboratory Test (Chemistry) Results

Population: Treated Population

Contents: Calculate summary statistics for the baseline, the lowest post-baseline level and the highest post-baseline level.

Calculate the patient numbers and percentages by shift in CTCAE grade from the baseline to the worst on-study result as follows:

- No change from baseline,
- Any worsening from baseline
- Worsening to grade 3 or grade 4
- <Grade 3 to grade 3
- <Grade 3 to grade 4
- Worsening to <grade 3
- Improved from baseline
- Unable to evaluate (note: missing at baseline or post-baseline)

10.2.3 Descriptive Statistics of Vital Signs

Population: Treated Population

Contents: Calculate the descriptive statistics for the baseline and the maximum post-baseline blood pressure.

Categorize patients according to the systolic and diastolic blood pressure and calculate the numbers of patients (and percentages) by shift from the baseline category to the worst post-

Population: Treated Population
baseline category.

Systolic blood pressure (mmHg)
<120
120 – 139
140 – 159
≥160

Diastolic blood pressure (mmHg)
<80
80 – 89
90 – 99
≥100

10.2.4 Descriptive Statistics of Left Ventricular Ejection Fraction (LVEF)

Population: Treated Population

Contents: Calculate the descriptive statistics for the baseline and the minimum post-baseline ejection fraction.

Calculate the patient numbers and percentages by shift in CTCAE grade from the baseline to the worst on-study result.

10.2.5 Descriptive Statistics of QTcF Interval

Population: Treated Population

Contents: Calculate the descriptive statistics for the baseline and the maximum post-baseline QTcF interval.

Categorize patients according to the baseline and the maximum post-baseline QTcF interval (<450ms, 450 - <480ms, 480 – <500ms, and ≥500ms). Calculate the numbers of patients (and percentages) by shift from the baseline category to the worst post-baseline category.

Calculate the descriptive statistics for the change from the baseline and the maximum post-baseline QTcF interval.

Categorize patients according to the change from the baseline to the maximum post-baseline level (<30 msec increase, 30-<60 msec increase, ≥60 msec increase, no change, decrease from baseline) and calculate the numbers of patients (and percentages) for each category.

11 CHANGE HISTORY

Version	Data	Author	Comments
1.0	2015/03/04	Ariad Pharmaceuticals Inc. PPD	Newly Created