Protocol B1871048

A Phase 2, Open-Label, Single-Arm Study to Evaluate Efficacy and Safety of Bosutinib Monotherapy in Japanese Adult Patients with Newly Diagnosed Chronic Phase Chronic Myelogenous Leukemia

Statistical Analysis Plan (SAP)

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[redacted]

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study B1871048 is based on the protocol dated 30MAR2018.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1 (24APR2017)	Not Applicable	Not Applicable
2 (23APR2018)	Section 2.1.2: • Added MMR by 12 months.	• To be consistent with the protocol.
•	Section 2.1.3: • Add a new sentence for MMR at 12 months; • Clarified time points for MR1 and MR2; • Removed the investigation of presence of newly observed BCR-ABL mutations.	• To be consistent with the protocol.
	Section 2.2: • Added the condition of target patient.	• To clarify the target patient.
	Section 3.2.1 • Added MMR by 12 months	• To be consistent with the protocol.
	Section 3.2.3: • Changed the reason of death as event; • Declared how to handle patients with suboptimal response; • Removed sentences about confirmation of CCyR.	• To be considered that death due to other than progressive disease is classified as the treatment discontinuation. • To explain how patients with suboptimal response are handled in analysis of the duration of response. • To avoid duplicated explanation.
	Section 3.2.4: • Removed an endnote; • Added a reference for loss of CCyR.	• To be consistent with the protocol. • To help a reader to confirm the definition.
	Section 3.3: • Added a new sentence for MMR at 12 months; • Clarified time points for MR1 and MR2; • Removed the investigation of presence of newly observed BCR-ABL mutations.	• To be consistent with the protocol.
	Section 3.4: • Defined the baseline.	• To clarify the baseline value.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
2 (23APR2018)	Section 3.5.2: • Added indirect bilirubin at endnote of liver function. Section 4.1: • Added a supplemental explanation. Section 5.1: • Changed the sentence about statistical test; • Added information about the rejection of null hypothesis. Section 5.2.2: • Added details of confidence interval. Section 5.2.3: • Added percentiles of cumulative incidence function. Section 5.3.1.5: • Corrected the condition considered a non-responder. Section 5.3.1.6: • Added MMR by 12 months. Section 6: • Added sentences how to handle patients without Ph+ or the b2a2/b3a2 transcript. Section 6.1.1.1: • Changed the word from the primary analysis to the primary efficacy analysis. Section 6.2.1: • Added MMR by 12 months. Section 6.2.3: • Added the proportion of patients with confirmed loss of response. Section 6.2.4: • Changed the referred method using EFS; • Clarified on-treatment EFS. Section 6.3.2: • Clarified time points for MR1 and MR2. Section 6.3.3: • Added yearly rates and percentiles.	• To declare that indirect bilirubin is out of analysis scope • To clarify that no analysis based on as-enrolled patients is conducted. • To describe the statistical assumption clearer. • To provide the reference for statistical test. • To describe the method of confidence interval using this study clearer. • To provide useful estimates. • To correct wrong information. • To be added MMR by 12 months in the protocol. • To clarify how a patient excluded from the modified as-treated is used in MMR or cytogenetic response. • To distinguish analyses at the interim look. • To be added MMR by 12 months in the protocol. • To be consistent with study AV001. • To correct the statistical method from Kaplan-Meier method to the cumulative incidence method. • To distinguish on-treatment EFS from off-treatment EFS. • To be consistent with the protocol. • To provide useful estimates.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
2 (23APR2018)	Section 6.3.4: • Clarified criteria for CHR using investigators and sponsor, respectively. Section 6.3.5: • Changed the referred method using time to transformation to AP/BP; • Clarified criteria for transformation to AP/BP using investigators and sponsor, respectively. Section 6.5: • Added the sentence related to analysis population. Section 6.5.2: • Added summary of patient disposition. Section 6.5.3: • Added summaries related to dose modification. Section 6.6.1: • Added new summaries; • Re-defined adverse event of special interest. Section 6.6.3: • Added criteria for potentially clinically important change. Section 6.6.4: • Added criteria for potentially clinically important change. Section 6.6.7: • Added summary of death. Section 7.1.1: • Added a new section for the interim look. Section 7.1.2: • Added a new section for the primary analysis. Section 7.1.4: • Added a new section for the periodic safety review. Section 7.2.1: • Added a new section for the interim look.	• To provide actually used criteria for investigator and the statistical analysis, respectively. • To correct the statistical method from Kaplan-Meier method to the cumulative incidence method. • To provide actually used criteria for investigator and the statistical analysis, respectively. • To avoid creating redundant TLFs. • To confirm patient disposition at 12 months. • To be consistent with study AV001. • To provide sufficient information about safety. • To be consistent with study AV001. • To be consistent with study AV001. • To be consistent with study AV001. • To provide details of death with reason. • To provide information about the interim look and to distinguish it from other 2 interim analyses. • To provide information about the primary analysis and to distinguish it from other 2 interim analyses. • To provide information about the periodic safety review and to distinguish it from other 2 interim analyses. • To provide timing, endpoints, hypotheses, statistical methods and prevention of bias in the interim look.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
2 (23APR2018)	Section 7.2.2: • Added a new section for the primary analysis. Section 7.2.4 • Added a new section for the periodic safety review. Appendix 1.3: • Removed sentences about protocol from the table footnote. Appendix 2: • Added a definition of adverse event of special interest. Appendix 3: • Added criteria for potentially clinically important changes. Appendix 4: • Added criteria for potentially clinically important changes.	• To provide timing and statistical methods in the primary analysis. • To provide timing and methods of review in the periodic safety review. • To be consistent with the protocol. • To be consistent with study AV001. • To be consistent with study AV001. • To be consistent with study AV001.
3 (09JUL2018)	Section 3.5.4.: • Removed a formula for QTcF; • Added a formula for QTcB; • Added a formula for heart rate. Section 6.2.6: • Corrected the document name of PK analysis plan. Section 6.3.5: • Added an analysis population. Section 6.3.6: • Added an analysis population. Section 6.5: • Added analysis populations. Section 7.2.1.2: • Added baseline variables. Section 7.2.1.4.4: • Added baseline variables. Section 7.2.1.5.7: • Added baseline variables.	• To be reported by a study site. • To provide a calculation of QTcB. • To provide a calculation of heart rate. • To make the referred document for PK analysis clear. • To make used analysis populations clear. • To make used analysis populations clear. • To make used analysis populations clear. • To provide baseline summaries in the interim look. • To provide information about used analysis populations for summarizing baseline variables. • To provide information about baseline summaries in the interim look.
4 (30JAN2019)	Section 3.2.4: • Added a condition for loss of CCyR. Section 5.3.6: • Added imputation method of Ph status at screening. Section 6.2.1: • Added timing of analysis for MMR by 18 months.	• To be consistent with the protocol. • To provide imputation method about the Ph status. • To avoid insufficient analysis due to immature data.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
	Section 6.2.4: • Added timing of analysis for off-treatment EFS. Section 6.3.1: • Added timing of analysis for MMR at 18 months. Section 6.5.3: • Added a summary item; • Clarified that a planned dose means a starting dose (ie, 400 mg). Section 6.6.1: • Added incidence of clustered anemia/neutropenia/thrombocytopenia/leukopenia; • Added some events into AE categories; • Added a listing of AEs included in each AESI; • Added a new figure of TEAE. Section 6.6.2.1: • Added a new section for an investigation of liver injury. Section 7.1.3: • Added a new section for a final analysis. Section 7.2.3: • Added a new section for a final analysis. Appendix 2: • Added definitions of some AESIs.	• To avoid insufficient analysis due to immature data. • To avoid insufficient analysis due to immature data. • To be consistent with study AV001. • To scientifically compare results of 3 penia in study 1048 with those in study AV001. • To be consistent with study AV001. • To provide which PT is categorized as an AESI. • To compare results in study 1048 with study AV001. • To evaluate a liver injury in Japanese patients. • To make the definition of final analysis clear. • To make endpoints summarized at the final analysis clear. • To scientifically compare results of 3 penia in study 1048 with those in study AV001.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B1871048. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives

2.1.1. Primary Objective

A primary study objective is to evaluate a major molecular response (MMR) at 12 months (48 weeks) in newly diagnosed Japanese Philadelphia chromosome (Ph)-positive (+) chronic phase (CP) chronic myelogenous leukemia (CML) patients harboring b2a2 and/or b3a2 transcripts.

2.1.2. Secondary Objectives

Secondary study objectives are:

- To evaluate MMR by 12 and 18 months;
- To estimate the proportion of patients demonstrating a complete cytogenetic response (CCyR) by 12 months;
- To evaluate the duration of MMR and CCyR;
- To evaluate an event-free survival (EFS);
- To evaluate overall survival (OS);
- To assess the population pharmacokinetic (PK);
- To assess correlations between trough concentrations of bosutinib and key efficacy and safety endpoints, and
- To characterize the safety profile of bosutinib in Japanese patients.

2.1.3. Exploratory Objectives

Exploratory study objectives are:

- To evaluate MMR at 3, 6, 9 and 18 months;
- To evaluate MMR at 12 months in patients with both Ph+ and Ph negative (-) CP CML;
- To evaluate molecular response (MR)[1] and MR[2] at 3 and 6 months, respectively;
- To evaluate $MR^{4.0}$ and $MR^{4.5}$ at 3, 6, 9 and 12 months;
- To evaluate time to MMR, $MR^{4.0}$, $MR^{4.5}$ and CCyR;
- To evaluate the proportion of patients demonstrating a cumulative complete hematologic response (CHR) in patients with Ph+ and both Ph+ and Ph- CP CML;
- To estimate the time to transformation to accelerated phase (AP) and blast phase (BP) CML on treatment;
- To evaluate the type of BCR-ABL* mutations present at treatment completion or discontinuation, or in case of suboptimal response, and

* Fusion transcript or protein resulting from the 9;22 chromosomal translocation responsible for formation of the Philadelphia Chromosome

- To enable exploratory research through collection of banked biospecimen, unless prohibited by local regulations or ethics committee (EC) decision.

2.2. Study Design

This is a phase 2, open-label, single-arm study designed to evaluate efficacy and safety of bosutinib alone in Japanese adult patients with newly diagnosed CP CML. Patients will receive bosutinib treatment at a starting dose of 400 mg once daily (QD). The dose of bosutinib is allowed to be escalated (up to a maximum of 600 mg QD) for unsatisfactory response or reduced for toxicity.

This study has approximately 52 weeks of planned patient accrual. Each patient will have 12 months (48 weeks) of Core Treatment Phase and the following ≥24 months (96 weeks) of Extension Phase. After treatment discontinuation, the patient enters Long-Term Follow-Up. The Extension Phase or Long-Term Follow-Up will continue until the end of the study.

The study will be open for enrollment until approximately 60 Ph+ CML patients with b2a2 and/or b3a2 transcripts have been registered. Bone marrow aspirate to assess the Ph status will be obtained at screening, patients with known Ph- prior to registration are not eligible for this study. However, as confirmation of the Ph status prior to registration is not mandatory, Ph- CML patients may also be included. Approximately 3 Ph- CML patients are expected to be registered as approximately 5% of the patients with BCR-ABL-positive CML are diagnosed as Ph- CML. All patients will be treated and/or followed up to approximately 3 years (144 weeks) after registration of the last patient, or until study termination, whichever comes first. Patients who permanently discontinue study treatment will be followed for survival, investigator-assessed transformation to AP/BP, duration of response and disease progression, and initiation/response to further anti-cancer therapies, including stem cell transplantation (where applicable).

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint

3.1.1. MMR at 12 Months

The primary endpoint is the MMR at 12 months (48 weeks). All Ph+ CP CML patients harboring b2a2 and/or b3a2 transcripts will be assessed and follow-up for the MMR as the primary endpoint.

The MMR is defined as ≤0.1% BCR-ABL on the international scale (IS) by quantitative reverse transcriptase polymerase chain reaction (RT-qPCR). See Appendix 1.1 for the details.

3.2. Secondary Endpoints

3.2.1. MMR by 12 and 18 Months

The MMR by 12-month and 18-month visit will be assessed.

3.2.2. CCyR

The CCyR by 12-month visit will be assessed.

The CCyR is defined as absence of detectable Ph. See Appendix 1.2 for the details.

3.2.3. Duration of MMR and CCyR

The duration of response (MMR and CCyR, respectively) is measured from the first date of response until the first date of confirmed loss of response, treatment discontinuation due to progressive disease (PD), or death due to PD within 28 days after last dose. A loss of response must be confirmed by a second consecutive loss at least 4 weeks later, treatment discontinuation due to PD or death due to PD within 28 days of last dose. A PD is defined as investigator assessed progression reported on the case report form (CRF). Treatment discontinuation due to PD or death due to PD within 28 days of last dose without loss of response will be considered a confirmed loss. An unconfirmed loss followed by treatment discontinuation due to suboptimal response is considered a confirmed loss.

For loss of MMR, the loss must be at least 5 times the smallest recorded ratio. Loss of CCyR is defined as at least one Ph+ metaphase.

Duration of response will be counted while a patient is on treatment. If treatment ceases and loss of response has not occurred, the patient will be censored at the last valid assessment on treatment for the respective endpoint.

3.2.4. EFS

The EFS is measured from the date of first dose until the first occurrence of one the following events, censored at the earlier of the last valid hematologic or cytogenetic assessment for those without events:

1. Death due to any cause;
2. Transformation to AP or BP (on treatment; see Appendix 1.3);
3. Loss of CHR.
    - Loss of CHR is defined as the appearance of any of the following, confirmed by a second determination ≥4 weeks later (unless associated with CML-related treatment discontinuation):
        - WBC count that rises to >20.0 × 10^9/L;
        - Pplatelet count that rises to ≥600 × 10^9/L;
        - Appearance of palpable spleen or other extramedullary involvement proven by biopsy;
        - Appearance of 5% myelocytes in the peripheral blood, or

- Appearance of blasts or promyelocytes in the peripheral blood.

4. Loss of CCyR (unless associated with CML-related treatment discontinuation; refer to Section 3.2.3 for the definition of loss of CCyR), or

5. For patients not achieving a CHR: doubling of white blood cell (WBC) at least 1 month apart with the second value >20 × 109/L and maintained in subsequent assessments for at least 2 weeks.

3.2.5. OS

OS is measured from the date of first dose until the occurrence of death due to any cause, censored at the last known alive date for those without events.

3.2.6. PK Endpoints

PK profiles of bosutinib will be determined using a sparse sampling regimen and population PK analysis approach. A total of 4 PK samples per patient will be drawn. All patients will provide pre-dose blood samples on Day 1, Day 28, Day 56, and Day 84.

PK endpoints and analyses include:

- Population PK of bosutinib, and
- Correlations between trough concentrations of bosutinib and key efficacy and safety endpoints.

3.3. Other Endpoints

The following endpoints will be assessed exploratorily:

- MMR at 3, 6, 9 and 18 months;
- MMR at 12 months in patients with both Ph+ and Ph- CP CML;
- MR^1 and MR^2 at 3 and 6 months, respectively;
- $MR^{4.0}$ and $MR^{4.5}$ at 3, 6, 9 and 12 months;
- Time to MMR, $MR^{4.0}$, $MR^{4.5}$ and CCyR;
- Cumulative CHR in patients with Ph+ and both Ph+ and Ph- CP CML;
- Time to transformation to AP and BP CML on treatment;
- Type of mutations present at treatment completion/discontinuation or suboptimal response;
- Potential results from exploratory analyses of banked biospecimen (these results may or may not be generated in the context of the present study).

3.4. Baseline Variables

The baseline will be defined as the last non-missing assessment prior to the first dose of study drug. An assessment on Day 1 is assumed to be pre-dose of study drug unless otherwise specified.

The following variables will be collected only during screening period:

- Demographics (gender, age and race);
- Sokal score;
- Medical and cancer history;
- Blood chemistry (hepatitis B virus (HBV) and hepatitis C virus (HCV) test);
- Height.

The age will be calculated as the number of elapsed years from date of birth to date of screening.

The Sokal score is derived by study sites using the following formula:

$$\exp(0.0116(\text{Age} - 43.4) + 0.0345(\text{Spleen} - 7.51) + 0.188((\text{Platelet} / 700)^2 - 0.563) + 0.0887(\text{Blasts} - 2.1)),$$

where units of Age, Spleen, Platelet and Blasts are years, centimeters below costal margin, 10^9/L and percentage of blasts in peripheral blood, respectively.

There are no stratification factors nor covariates in this study.

3.5. Safety Endpoints

Safety endpoints are the secondary endpoints in this study.

3.5.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a study patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage.

A treatment-emergent adverse event (TEAE) is defined as an AE that first occurred or worsened in severity from the first dose of the study drug until 28 days after the last dose. TEAEs will be assessed mainly in this study.

3.5.2. Laboratory Data

The following laboratory parameters will be assessed:

- Complete blood count (CBC) including WBC count with 5-part differential, absolute neutrophil count (ANC), platelet count, red blood cell (RBC) count and hemoglobin;

- Liver function measurements† including aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin;

- Blood chemistry including sodium, potassium, chloride, carbon dioxide or bicarbonate (if available), blood urea nitrogen (BUN) or urea, creatinine, glucose, total protein, albumin, calcium, alkaline phosphatase, amylase, lipase, phosphorous, magnesium, creatine kinase and uric acid (until patient achieves CHR);

- Coagulation test including prothrombin time (PT) or international normalized ratio (INR) and partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT);

- Urinalysis including urine protein and urine blood, and

- Estimated glomerular filtration rate (eGFR) calculated by study sites using the following Modification of Diet in Renal Disease (MDRD) formula;

  $32788 \times (\text{Creatinine} / 88.4)^{-1.154} \times \text{Age}^{-0.203} \times 0.742$ (if female) $\times$ 1.21 (if black).

3.5.3. Vital Signs and Body Weight

Temperature (axillary), supine blood pressure, heart rate and body weight will be assessed.

3.5.4. Electrocardiograms

Triplicate 12-lead (with a 10 second rhythm strip) tracings will be used for all electrocardiograms (ECGs). A QT interval will be corrected for an RR interval using Fridericia's (QTcF) and Bazett's factors (QTcB), respectively. Actually, QTcF will be reported by study sites. On the other hand, QTcB will be derived from $QT / RR^{1/2}$. A heart rate will be derived from 60000 / RR if the unit of RR is msec.

At each time point, 3 consecutive ECGs will be performed at approximately 2 minutes apart to determine the mean QTcF and QTcB intervals.

3.5.5. Echocardiogram or Multiple Gated Acquisition

Echocardiogram (ECHO) or multiple gated acquisition (MUGA) will be performed at screening (within 2 weeks prior to registration) and at End of Treatment/Withdrawal or at Week 96, whichever is earlier, and as clinically indicated.

† Direct and indirect bilirubin are specified in the study protocol to evaluate the liver function as needed. However, the result of measurement will not be collected in the CRF. Therefore, they are removed from the SAP.

4. ANALYSIS SETS

Data for all patients will be assessed to determine if patients meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per standard operating procedures.

4.1. As-Treated Population

The as-treated population will consist of all enrolled patients who received at least 1 dose of study drug. Since this is a single-arm phase 2 study, as-treated population is also the full analysis set.

4.2. Modified as-Treated Population

The modified as-treated population will consist of all enrolled patients with Ph+ CP CML harboring b2a2 and/or b3a2 transcripts who received at least 1 dose of study drug.

4.3. Safety Analysis Set

The safety population will consist of all enrolled patients, regardless of Ph status, who received at least 1 dose of study drug. This means that the as-treated population is also the safety analysis set. Therefore, the as-treated population will be presented in any tables, listings and figures instead of the safety analysis set.

4.4. PK Analysis Set

The PK population will be defined as any patient in the safety population of patients who had at least 1 concentration of bosutinib on-treatment.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

In this study, null (H_0) and alternative (H_1) hypotheses are as follows:

H_0: the true MMR rate at 12 months (48 weeks) is 25%;

H_1: the true MMR rate at 12 months (48 weeks) is 40%.

With 60 Ph+ patients, the study is powered at greater than 82% to test this null versus alternative hypothesis with one-sided alpha of 5%. The MMR rate at 12 months will be considered >25% if and only if the null hypothesis is rejected (observing at least 21 responders [35%] out of the 60 total patients). The statistical comparison will be performed after Core Treatment Phase of all treated patients. No multiplicity adjustment will be needed.

No formal statistical hypothesis tests will be performed for any endpoints except for the primary endpoint.

5.2. General Methods

5.2.1. Analyses for Continuous Data

Continuous data will be summarized descriptively (n, mean, standard deviation, minimum, median, maximum) unless otherwise specified.

5.2.2. Analyses for Categorical Data

Categorical data will be summarized using the frequency table (the number of patients, frequency and percentage). An asymptotic confidence interval (CI) of estimated proportion for response rate will also be presented as needed.

5.2.3. Analyses for Time-to-Event Data

Time-to-event data (duration of response and OS) will be summarized using the Kaplan-Meier method and estimated survival curves will be displayed graphically when appropriate. Graphs will describe the number of patients at risk over time. The median, quartiles and probabilities of an event at particular points in time will be estimated by the Kaplan-Meier method. CIs for medians and quartiles are based on the Brookmeyer-Crowley method. CIs for the estimated probability of event at a particular time point will be generated using the Greenwood's formula. When applying the cumulative incidence method (time to response and transformation, EFS),[1] yearly rates with the associated CI based on delta method with log(-log) transformation method will be provided. Percentiles of the cumulative incidence function (25%, 50% and 75%) will also be provided.

5.3. Methods to Manage Missing Data

5.3.1. Molecular Response Assessment

5.3.1.1. MMR, $MR^{4.0}$ and $MR^{4.5}$ at 12 months (48 weeks)

If a patient is missing a molecular response assessment at 48-week visit, and patient demonstrates response at both the 36-week and 60-week visits, then that patient will be considered a responder at the 48-week visit. In other situation, a patient will be considered a non-responder at the 48-week visit.

5.3.1.2. MMR at 18 months (72 weeks)

The same rules apply for MMR at 18 months as they do for MMR at 12 months. In this case, the 60-week and 84-week visits will be used for a missing molecular assessment.

5.3.1.3. MR^1 and MR^2 at 3 and 6 months

If a patient is missing the assessment, they will be coded as a non-responder.

5.3.1.4. MMR, $MR^{4.0}$ and $MR^{4.5}$ at 3 month

If a patient is missing the assessment, they will be coded as a non-responder.

5.3.1.5. MMR, $MR^{4.0}$ and $MR^{4.5}$ at 6 and 9 months

If a patient is missing a molecular response assessment at the time of interest and the patient demonstrates molecular response at both prior and subsequent visits, then that patient will be considered a responder at that time of interest. If a patient is missing molecular response at either prior or subsequent visits, then that patient will be considered a non-responder at that time of interest.

5.3.1.6. MMR by 12 and 18 months (48 and 72 weeks)

If a patient is missing a molecular response at the 48-week and 72-week visits and the patient has demonstrated a MMR at visits prior to the 48-week and 72-week visits, then the patient will be considered a responder by the 48-week and 72-week visits, respectively.

5.3.2. Cytogenetic Response Assessment

Handling of missing bone marrow data will take the following steps:

1. If bone marrow cytogenetics results are not available and a MMR is achieved on a specific date, then a CCyR response will be imputed for that date.

2. If bone marrow cytogenetics results are available where <20 metaphases analyzed with zero Ph+ cells and a MMR is achieved on a specific date, then a CCyR response will be imputed for that date.

5.3.3. Hematologic Response Assessment

Handling of missing hematology data will take the following steps:

1. For each patient, the observations are sorted by visit and the relative day.

2. For each observation, the peripheral blood differentials should add up to 100%. Some sites may not record 0%. Instead, the corresponding field may appear as missing or "ND." If myelocytes, promyelocytes and myeloblasts in the blood differential are reported as missing or "ND," the following rule will be applied. Each domain of the differentials will be summed together. If the total is between 98.5% and 101%, the missing values will be assigned 0%. Otherwise, the observation will be left as is and the record will also be reported as a data issue.

3. If CHR cannot be assessed due to one or more missing components of CHR, impute CHR if a patient has a MMR or a CCyR and all assessed components of CHR are within appropriate limits.

Furthermore, in the absence of extramedullary disease info, it is assumed that spleen is non-palpable.

5.3.4. Time-to-Event Data

The primary missing data handling method will be censoring. A patient withdrawing from the study without experiencing the event of interest will be censored at the last valid (ie, evaluable) assessment of that event. A patient who fails on treatment, after missing two or more assessments of both hematologic and cytogenetic response, will be censored for on-treatment EFS at the last hematologic or cytogenetic assessment. A patient, who dies after treatment discontinuation during long-term follow-up and after missing two or more long-term follow-up assessments, will be censored for off-treatment EFS at the last assessment at which the patient was found to be alive and event-free. See also Section 3.2.3 for duration of MMR or CCyR.

5.3.5. Safety Endpoints

Missing safety data will be handled according to Pfizer standards.

5.3.6. Other Variables

For a patient without an available Ph status data at screening, cytogenetics data of the patient at Month 3 will be impute as the Ph status at screening only if a study monitor is able to confirm the Ph status before screening and records it in an appropriate document such as a monitoring record.

Other variables except for endpoints described in Section 5.3 will not be imputed.

6. ANALYSES AND SUMMARIES

All efficacy analyses will be performed using the modified as-treated population unless otherwise specified. In case the as-treated population is completely the same as the modified as-treated population, analyses for efficacy endpoints using the as-treated population may be omitted.

Patients without the b2a2 or b3a2 transcript will be counted as non-responders of MMR in the as-treated population. Analyses including cytogenetic data will only be performed on the modified as-treated population as Ph- patients are not assessable for cytogenetic response.

6.1. Primary Endpoint

6.1.1. MMR at 12 Months

6.1.1.1. Primary Efficacy Analysis

The MMR at 12 months (48 week) will be analyzed using the hypothesis test of a one-sample binomial proportion test with the normal approximation (also refer to Section 5.1). The two-sided 90% CI of MMR rate at 12 months (48 weeks) will also be calculated.

The MMR at 12 months (48 weeks) is counted only if the response is demonstrated at the 12-month (48-week) visit; any MMR gained and lost before the 12-month (48-week) visit is deemed a non-response as is the case where the MMR is never achieved at or before 12 months (48 weeks).

The modified as-treated population will be used in the primary efficacy analysis.

6.2. Secondary Endpoints

6.2.1. MMR by 12 and 18 Months

Evaluations of MMR by 12 and 18 months will be assessed using the frequency tables, respectively. The two-sided 90% CI will also be calculated. For the analysis of MMR by 12 and 18 months, a patient is counted as a responder if the MMR occurs at or before 12 and 18 months, respectively, even if the MMR is subsequently lost at or before the 12-month and 18-month time point, respectively. A patient never achieving the MMR at or before 12 and 18 months will be considered a non-responder, respectively.

The MMR by 18 months will only be summarized at the final analysis (FA; refer to Section 7.2.3 with respect to the FA).

6.2.2. CCyR

Evaluations of CCyR by 12 months (48 weeks) will be assessed using the frequency tables. The two-sided 90% CI will also be calculated. The CCyR rate by 12 months is defined as the proportion of patients demonstrating CCyR at or before 12 months (48 weeks). The percentage of Ph+ cells will be calculated according to the following formula:

$$\text{ceil}(100 \times \text{the number of Ph+ cells} / \text{the number of metaphases}),$$

where ceil() denotes a ceiling function.

The proportion of patients who have confirmed loss of CCyR will also be evaluated.

6.2.3. Duration of Response

The duration of MMR and CCyR will be based on the estimations of the quartiles of duration and yearly rates using the Kaplan-Meier method.

For the analysis of MMR and CCyR, the proportion of patients who have confirmed loss of response will also be evaluated, respectively.

The duration of MMR will be analyzed for MMR responders in the modified as-treated population and those in as-treated population separately. The duration of CCyR will be analyzed for CCyR responders in the modified as-treated population.

6.2.4. EFS

EFS will be analyzed using the cumulative incidence method[1] adjusting for the competing risk of treatment discontinuation without the event, and yearly rates and percentiles will be displayed. This will be indicated as the on-treatment EFS. As a definition of "on-treatment" is described in Section 6.3.5, the transformation to AP and BP on treatment will be considered as an event in the analysis of EFS. This means that if the first transformation to AP and BP is occurred after 28 days from the last dose, this will not be considered as an event in the analysis of EFS.

As a reference, the EFS using the transformation to AP and BP occurred after 28 days from the last dose instead of the transformation to AP and BP on treatment will also be assessed using the same analysis method. This will be indicated as the off-treatment EFS.

The on-treatment EFS and off-treatment EFS will be analyzed in the modified as-treated population.

The off-treatment EFS will only be evaluated at the FA (refer to Section 7.2.3 with respect to the FA).

6.2.5. OS

The analysis of OS will be similar to that for duration of response just described.

The OS will be analyzed in the modified as-treated population and as-treated population separately.

6.2.6. Pharmacokinetics

PK profiles of bosutinib will be determined using a sampling regimen and population PK analysis approach. A total of 4 PK samples per patient will be drawn. All patients in the bosutinib treatment group will provide pre-dose blood samples on Day 1, 28, 56 and 84.

Concentrations of bosutinib will be determined in plasma using a Sponsor-approved and validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) assay.

The objectives of the population PK analysis are 1) to develop a population PK model which describes the PK of bosutinib in this patient population, 2) to evaluate the influence of demographic and clinical covariates on the exposure of bosutinib, and 3) to explore the relationship between trough concentrations of bosutinib with clinical safety (drug related adverse effects such as GI AEs, and any other major AEs) and efficacy endpoints.

The concentration of study drug will be analyzed using population PK methodology. Population mean values of PK parameters (eg, clearance [CL/F], volume of distribution [V/F]) will be estimated. PK relationships between plasma study drug concentration and selected outcome measures will be characterized using a population approach.

Details of analysis of PK endpoints is referred to "B1871048 Pharmacokinetic Analysis Plan", which is separetely developed.

6.3. Other Endpoint(s)

6.3.1. MMR at Each Pre-Specified Visit

Measures of MMR at 3, 6, 9, 12 and 18 months will be evaluated by frequency tables. The two-sided 90% CI will also be calculated.

These analyses except for the MMR at 12 months will be performed using the modified as-treated population and as-treated population, respectively.

The exploratory MMR analysis at 12 months will be analyzed for the as-treated population.

The MMR at 18 months will only be summarized at the FA (refer to Section 7.2.3 with respect to the FA).

6.3.2. Molecular Response

Measures of MR^1, MR^2, $MR^{4.0}$ and $MR^{4.5}$ at each pre-specified visit will be evaluated by frequency tables. The two-sided 90% CI will also be calculated.

Pre-specified visits for MR^1 and MR^2 are 3 and 6 months, respectively, while pre-specified visits for $MR^{4.0}$ and $MR^{4.5}$ are 3, 6, 9 and 12 months.

These analyses will be performed using the modified as-treated population and the as-treated population, respectively.

6.3.3. Time to MMR, CCyR, $MR^{4.0}$ and $MR^{4.5}$

The time to response (MMR, CCyR, $MR^{4.0}$, and $MR^{4.5}$) is measured from first dose to the first date of response. The time to response will be analyzed using the cumulative incidence method.[1] Yearly rates and percentiles will be displayed. In the analysis of cumulative incidence (see Section 5.2.3), the competing risk is defined as treatment discontinuation without response. Also, other patients without response will be censored at the last valid assessment for the respective endpoint.

The time to response will be also summarized by descriptive statistics among responding patients.

The time to MMR, $MR^{4.0}$ and $MR^{4.5}$ will be analyzed for the modified as-treated population and as-treated population separately. The time to CCyR will be calculated using the modified as-treated population.

6.3.4. Cumulative CHR

Evaluations of cumulative CHR will be assessed using the frequency tables. The two-sided 90% CI will also be calculated.

The cumulative CHR will be analyzed for the modified as-treated population and as-treated population separately.

Investigators should assess hematologic response according to the original definition of CHR (see Appendix 1.4). In a statistical analysis, some restrictions (see table footnotes in Appendix 1.4) are adopted in addition to the original definition.

6.3.5. Time to Transformation to AP and BP CML

The analysis of the time to transformation to AP and BP CML will be similar to that of the time to response described above.

The time to transformation to AP and BP CML is defined as the time from first dose to the first date of transformation to AP or BP CML. The transformation to AP and BP will be counted while a patient is on treatment up to 28 days after last dose. In the analysis of cumulative incidence[1] (see Section 5.2.3), the competing risk is defined as treatment discontinuation without transformation. If transformation has not occurred, the patient will be censored at the last valid hematologic assessment.

Investigators should assess transformation to AP/BP according to the original definition of AP/BP CML (see Appendix 1.3). In a statistical analysis, some restrictions (see table footnotes in Appendix 1.3) are adopted in addition to the original definition.

Time to transformiation to AP and BP CML will be analyzed for the modified as-treated population and as-treated population separately.

6.3.6. Mutations

Types of BCR-ABL mutations present at treatment completion and when performed during treatment will be summarized by frequency tables.

Summaries of newly observed BCR-ABL mutations in patients post-baseline will be presented by visit.

Types of BCR-ABL mutations will be summarized using the modified as-treated population and as-treated population separately.

6.4. Subset Analyses

Subgroup analyses using Sokal score for MMR at 12 months (48 weeks) will be performed and two-sided 90% CIs will be presented. Sokal score will be categorized as follows:

- Low risk: Sokal score <0.8;
- Intermediate risk: Socal score 0.8 to 1.2, and

- High risk: Sokal score >1.2.

This analysis will be evaluated for the modified as-treated population and the as-treated population, respectively.

6.5. Baseline and Other Summaries and Analyses

Both as-treated population and modified as-treated population will be used unless otherwise specified. In case the as-treated population is completely the same as the modified as-treated population, summaries using the modified as-treated population may be omitted.

6.5.1. Baseline Summaries

Baseline variables including the body weight and Ph status at the screening period will be summarized descriptively for both the modified as-treated population and the as-treated population according to Section 5.2.1 and Section 5.2.2., respectively. The body mass index will be derived using the height and body weight at the screening period and will be reported as a baseline variable.

6.5.2. Study Conduct and Patient Disposition

The total number of enrolled patients, the number of patients who completed/discontinued the treatment/study and the reason for any premature discontinuation from the treatment/study will be presented. In addition, the number of patients who completed the treatment to 12 months and discontinued the treatment within 12 months will be presented. The number of patients in each analysis set also be presented.

6.5.3. Study Treatment Exposure

Exposure to study drug will be evaluated by duration of treatment exposure (the number of doses and missed doses) for as-treated population. In addition, actual dose intensity, and relative dose intensity will be evaluated. Descriptive statistics will be presented for continuous exposure variables: treatment duration (the number of days on treatment), actual dose intensity, and relative dose intensity. The frequency and percentage of patients with at least one dose reduction due to AE, temporally stopped study drug due to AE, reduction to 300 and 200 mg, and escalation to 500 and 600 mg will also be summarized. Further, the followings will be summarized:

- Number of dose delay;
- Number of dose reduction;
- Number of dose escalation;
- Time to the first dose delay;
- Duration of dose delay;
- Time to the first dose reduction;

- Duration of dose reduction, and
- Time to the first dose escalation.

Cumulative dose (unit: mg) will be calculated as the summation of all administered doses.

Duration of treatment will be calculated as

$$\text{Duration of Treatment (days)} = DL - DF + 1;$$

where

DL: the date of the last non-zero dose of the study drug, and

DF: the date of the first non-zero dose of the study drug.

Actual dose intensity (unit: mg/day) will be calculated as

$$\text{Actual dose intensity (mg/day)} = aCD / (LDD - DF + 1),$$

where

aCD: actual cumulative dose in mg;

LDD: the last dose date of zero or non-zero dose of the study drug, and

DF: the date of the first non-zero dose of the study drug.

Theoretical dose intensity (unit: mg/day) will be calculated as:

$$\text{Theoretical dose intensity (mg/day)} = pCD / (LDD - DF + 1).$$

where

pCD: planned cumulative dose (ie, cumulative starting dose) in mg;

LDD: the last dose date of zero or non-zero dose of the study drug, and

DF: the date of the first non-zero dose of the study drug.

Relative dose intensity will be calculate according the following formula:

$$\text{Relative dose intensity (\%)} = 100 \times (\text{Actual dose intensity}) / (\text{Theoretical dose intensity}).$$

6.5.4. Concomitant Medications and Non-Drug Treatments

Summary of concomitant medications will include the frequency and percentage of patients by Anatomical Therapeutic Chemical (ATC) Classification level 2 and preferred term. In case any specific medication does not have ATC classification level 2 coded term, it will be summarized under “Unavailable ATC classification” category.

Summary of non-drug treatments will include the frequency and percentage of patients by Medical Dictionary for Regulatory Activities (MedDRA) preferred term.

6.5.5. Transfusions

Summary of transfusions will include the frequency and percentage of patients by the transfusion type.

6.5.6. ECOG Performance Status

Summary of ECOG performance status will include the frequency and percentage of patients at each visit.

6.5.7. Extramedullary Disease

Summary of extramedullary disease will include the frequency and percentage of patients at each visit by body sites.

6.5.8. Chest X-ray

Results of chest X-ray will be summarized descriptively at each visit.

6.6. Safety Summaries and Analyses

All safety analyses will be performed using the as-treated population.

6.6.1. Adverse Events

All AEs will be coded using the latest version of MedDRA dictionary at the analysis. The toxicity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.

The numbers of events and incidence rates will be tabulated by preferred term and system organ class. AEs will be presented with and without regard to causality. The frequency of overall toxicity, categorized by toxicity Grades 1 through 5, will be described. Additional tables will be provided for AEs that are observed with higher frequency.

AE summaries will include incidence of TEAEs by MedDRA preferred term and system organ class, incidence of clustered anemia/neutropenia/thrombocytopenia defined in Appendix 2 and clustered leukopenia includeing PTs in leukopenia and white blood cell count decreased, SAEs including deaths, AEs that led to study drug discontinuation, characteristics of AEs that led to study drug discontinuation, AEs that led to study drug interruption, AEs that led to study drug reduction and AEs by maximum severity and relationship to study drug. Discontinuation due to AE and death data will also be listed.

AEs and AE categories including cardiac, oedema, effusion, gastrointestinal, diarrhea, nausea, vomiting, hemorrhage, anemia, neutropenia, thrombocytopenia, hypersensitivity, hypertension, infection, liver function, ALT, AST, myelosuppression, rash, renal and vascular will be summarized (see Appendix 2). A listing of AEs included in each AESI category will be provided by each patient.

TEAEs leading to death within 28 days of the last dose will be summarized.

Percentage of subjects with TEAEs (diarrhea, ALT, AST and the first onset of diarrhea) by maximum grade will be plotted using a cumulative bar chart at each month.

6.6.2. Laboratory Data

Laboratory results including bone marrow aspirate will be classified according to the NCI CTCAE version 4.03. Laboratory results that are not part of NCI CTCAE or are impossible to be classified according to the NCI CTCAE using laboratory data only will be presented according to the categories: below normal limit, within normal limits and above normal limit (according to the laboratory normal ranges). Kidney Disease Improving Global Outcomes (KDIGO) categories (see Appendix 1.5) will be used for eGFR grading.

Laboratory assessments will be presented as mean changes from baseline and incidence of abnormal values. Shift tables will also be presented.

6.6.2.1. Hy's Law

Abnormal values in AST and/or ALT concurrent with abnormal elevations in total bilirubin that met the criteria outlined below in the absence of other causes of liver injury will be considered potential cases of drug induced liver injury (potential Hy's Law cases).

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently presented with AST or ALT >3 x upper limit of normal (ULN) concurrent with a total bilirubin >2 x ULN with no evidence of hemolysis and an alkaline phosphatase <2 x ULN or not available.

- For subjects with pre-existing ALT or AST or total bilirubin values above the ULN, the following threshold values were used in the definition mentioned above.

  For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT >2 times the baseline values and >3 x ULN, or >8 x ULN (whichever was smaller).

  For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin increased by 1 x ULN or >3 x ULN (whichever was smaller).

The potential Hy's law will be confirmed at each time point. Further, an evaluation of drug-induced serious hepatotoxicity (eDISH) scatter plot of peak ALT, peak AST and peak ALT/AST versus peak total bilirubin will be presented.

6.6.3. Vital Signs and Body Weight

Vital signs (temperature (axillary), supine blood pressure and heart rate) and body weight will be presented using descriptive statistics. Criteria for potentially clinically important changes is shown in Appendix 3.

6.6.4. ECG

Actual values and changed from baseline of all measured ECG parameters (an average of the triplicate measurements) will be presented using descriptive statistics. Frequencies and percentages of patients with potentially clinically important changes in ECG will be summarized. Criteria for potentially clinically important changes is shown in Appendix 4.

6.6.5. Echocardiogram or Multiple Gated Acquisition

Echocardiogram or multiple gated acquisition will be presented using descriptive statistics.

6.6.6. Physical Examination

Summary of physical examination will include the frequency and percentage of patients at the screening period by body sites. Presence or absence of any change from the screening will also be summarized using descriptive statistics at each post-screening visit.

6.6.7. Death

Deaths during the study and within 28 days from the last dose will be summarized by reason for death. Relevant information will also be supplied in a data listing. Deaths occurring beyond 28 days from the last dose will be included in a data listing.

7. INTERIM ANALYSES

7.1. Introduction

7.1.1. Interim Look

An interim look (IL) will be conducted separately prior to the PA to assess the possibility of early communication with regulatory authorities based on the interim data. This will not be used to judge the early study termination or any changes of study design. The IL is planned only once in this study and the primary endpoint will not be analyzed.

7.1.2. Primary Analysis

The PA will be performed:

- To verify whether the study goal is achieved, and
- To submit study data to a regulatory authorities if the study drug is considered to show efficacy and tolerable.

All planned analyses will be performed at the PA unless otherwise specified. The PA is planned only once in this study. This study will not use a data monitoring committee.

7.1.3. Final Analysis

The FA will be performed at the end of study. Before the FA, all data will be cleaned and the database will be locked/released. Some specified endpoints will be summarized newly or updated from the PA at the FA.

7.1.4. Periodic Safety Review

For the purposes of this study, Pfizer procedures for periodic safety review will be applied by an internal safety review team with medical and statistical capabilities.

7.2. Interim Analyses and Summaries

7.2.1. Interim Look

7.2.1.1. Timing of the Interim Look

The IL will occur at 3 months after the first dose of the last patient.

7.2.1.2. Endpoints

The following endpoints for patients with sufficient follow-up will be summarized at the IL:

- Cumulative incidence of MMR at 12 months;
- MMR by 12 months;
- MMR at 3, 6 and 9 months;
- MR[1] at 3 months;
- all safety endpoints;
- All PK endpoints except for primary endpoint related parameters (Exposure-Response relationship will not be included in the interim data.), and
- Baseline variables.

Analysis of primary endpoint will not be conducted at the IL.

7.2.1.3. Hypotheses

No statistical hypothesis test will be performed. Therefore, no alpha will be spent at the IL.

7.2.1.4. Analysis Sets

7.2.1.4.1. Efficacy

For efficacy endpoints, the modified as-treated population will be used at the IL. In addition, a specified subset of the modified as-treated population shown below will also be used in each endpoint if specified.

Endpoints	Subset Criteria
• Cumulative incidence of MMR at 12 months • MMR by 12 months	• For the patient continuing the study treatment, the assessment at 12 months is completed. • For the patient discontinuing the study treatment, at least 332 days after the first dose of study drug in the patient have passed at the IL.

Endpoints	Subset Criteria
• MMR at 6 months	• For the patient continuing the study treatment, the assessment at 6 months is completed. • For the patient discontinuing the study treatment, at least 164 days after the first dose of study drug in the patient have passed at the IL.
• MMR at 9 months	• For the patient continuing the study treatment, the assessment at 9 months is completed. • For the patient discontinuing the study treatment, at least 248 days after the first dose of study drug in the patient have passed at the IL.

7.2.1.4.2. Safety

For safety endpoints, the as-treated population will be used at the IL.

7.2.1.4.3. PK

For PK endpoints, the PK analysis set will be used at the IL.

7.2.1.4.4. Baseline Variables

For baseline variables, the as-treated population and the modified as-treated population will be used at the IL.

7.2.1.5. Analysis Methods

7.2.1.5.1. Cumulative Incidence of MMR at 12 Months

The cumulative incidence of MMR at 12 months will be estimated using the cumulative incidence method described in Section 6.3.3.

7.2.1.5.2. MMR by 12 Months

The MMR by 12 months will be summarized described in Section 6.2.1.

7.2.1.5.3. MMR at 3, 6 and 9 Months

The MMR at 3, 6 and 9 months will be summarized described in Section 6.3.1.

7.2.1.5.4. MR[1] at 3 Months

The MR[1] at 3 months will be summarized described in Section 6.3.2.

7.2.1.5.5. Safety Endpoints

All safety endpoints will be summarized described in Section 6.6.

7.2.1.5.6. PK Endpoints

All PK endpoints (excluding the Exposure-Response relation) will be summarized described in Section 6.2.6.

7.2.1.5.7. Baseline Variables

Baseline variables will be summarized described in Section 6.5.

7.2.1.6. Prevention of Any Bias

The results from the IL will not be reported to the study monitors and site staff including investigators to prevent the mixture of any bias.

7.2.2. Primary Analysis

The PA will be conducted after Core Treatment Phase of all treated patients and before the FA. All analyses described in this SAP including the primary efficacy analysis of the primary endpoint will be performed at the PA unless otherwise specified. No adjustment of the significance level will be needed because no formal analysis is planned at the FA.

7.2.3. Final Analysis

The FA will be conducted after releasing the study database. The endpoints described below will be reported at the FA.

- MMR by 18 months;
- Duration of MMR and CCyR;
- EFS (both on-treatment and off-treatment);
- OS;
- MMR at 18 months;
- Time to MMR, $MR^{4.0}$, $MR^{4.5}$ and CCyR;
- Time to transformation to AP and BP CML on treatment;
- Type of mutations present at treatment completion/discontinuation or suboptimal response;
- All safety endpoints.

No statistical hypothesis test will be planned at the FA.

7.2.4. Periodic Safety Review

The team will review individual and summary data collected in the safety and clinical databases for periodic safety review.

8. REFERENCES

1. Lin G, So Y, Johnston G. Analyzing survival data with competing risks using SAS® Software. Proceedings of the SAS® Global Forum 2012 Conference; 22-25 Apr 2012; Cary, NC: SAS Institute; 2012.

9. APPENDICES

Appendix 1. Response Definitions

Appendix 1.1. Molecular Responses

Before Treatment	Molecular Response	RT-PCR (BCR-ABL Ratio)
Chronic Phase	Major, or MMR	≤0.1% (corresponding to ≥3 log reduction from baseline[a]) with a minimum number of ABL transcripts specified by the central laboratory
	MR[1]	A 1 log reduction in BCR-ABL transcript with a minimum number of ABL transcripts specified by the central laboratory
	MR[2]	A 2 log reduction in BCR-ABL transcript with a minimum number of ABL transcripts specified by the central laboratory
	MR[4.0]	Either (i) detectable disease with ≤0.01% BCR-ABL IS or (ii) undetectable disease in cDNA with a minimum number of ABL transcripts specified by the central laboratory
	MR[4.5]	Either (i) detectable disease with ≤0.0032% BCR-ABL IS or (ii) undetectable disease in cDNA with a minimum number of ABL transcripts specified by the central laboratory in the same volume of cDNA used to test for BCR-ABL

a. Standardized baseline from central laboratory.

Appendix 1.2. Cytogenetic Responses

Before Treatment	Cytogenetic Responses[a]	Percent of Ph+ Cells
Chronic Phase	None	>95%
	Minimal	66%–95%
	Minor	36%–65%
	Partial	1%–35%
	Complete	0%
	Major	Complete + Partial Rates

a. Based on analysis of at least 20 metaphases.

Appendix 1.3. Blast Phase and Accelerated Phase

Patient meeting any of the following criteria will be judged as either a BP or an AP.

Phase	Criteria
Blast Phase	• ≥30% blasts in blood or bone marrow. • Extramedullary blast proliferation, other than in spleen.
Accelerated Phase	• 15%–29% blasts in blood or marrow, or >30% blasts plus promyelocytes in blood or marrow with blasts <30%. • ≥20% basophils in blood. • Persistent thrombocytopenia (<100 × 10^9/L) unrelated to therapy[a]. • Clonal chromosome abnormalities in Ph+ cells (CCA/Ph+), major route, on treatment[b].

a. Persistent thrombocytopenia is not considered to define AP progression as the database does not collect data regarding the relationship between the platelet value and therapy.
b. Clonal chromosome abnormalities alone are not considered sufficient to define progression to AP unless concurrent presence of another AP criterion.

Appendix 1.4. Hematologic Responses

Hematologic Responses[a]	Definition
Complete Hematologic Response, or CHR	• WBC ≤10 × 10^9/L. • Basophils <5% in blood. • No myelocytes, promyelocytes, myeloblasts in the blood differential. • Platelet count <450 × 10^9/L. • Spleen non palpable[b].

a. Had to meet all criteria indicated in the Definition column
b. In the absence of extramedullary disease info, it is assumed that that spleen is non-palpable.

Appendix 1.5. KDIGO Categories

eGFR Category	eGFR (ml/min/1.73 m^2)	Terms
1	≥90	Normal or high
2	60–89	Mildly decreased
3a	45–59	Mildly to moderately decreased
3b	30–44	Moderately to severely decreased
4	15–29	Severely decreased
5	<15	Kidney failure

Appendix 2. Adverse Event of Special Interest

The table below is presented criteria for adverse event of special interest. This was actually used in the study AV001. Though AE criteria listed below were defined using MedDRA version 19.0, the latest version of MedDRA at the time of analysis will be used. Therefore, criteria may possible be updated. Actual criteria used in this study will be reported in the clinical study report.

AE Category	AE Criteria
Cardiac	• HLGTs in Cardiac arrhythmias, Heart failures, Pericardial disorders. • PTs in Cardiac death, Sudden cardiac death, Sudden death, Ejection fraction decreased. • MedDRA SMQ (Narrow): Torsade de pointes/QT prolongation.
Oedema	• PTs contain Oedema, Weight increased.
Effusion	• PTs in Pleural effusion, Pericardial effusion.
Gastrointestinal	• PTs in Nausea, Regurgitation, Retching, Vomiting, Vomiting projectile, Diarrhoea, Defaecation urgency, Frequent bowel movements, Gastrointestinal hypermotility.
Diarrhoea	• PT in Diarrhoea.
Nausea	• PT in Nausea.
Vomiting	• PT in Vomiting.
Hemorrhage	• PTs in Gastric occult blood positive, Occult blood positive. • MedDRA SMQ (Narrow): Haemorrhage terms (excl laboratory terms).
Anemia	• PTs in Anaemia, Hemoglobin decreased.
Neutropenia	• PTs in Neutropenia, Neutrophil count decreased.
Thrombocytopenia	• PTs in Thrombocytopenia, Platelet count decreased.
Hypersensitivity	• HLGT in Allergic conditions.
Hypertension	• HLGT in Vascular hypertensive disorders. • PTs in Blood pressure abnormal, Blood pressure ambulatory abnormal, Blood pressure ambulatory increased, Blood pressure diastolic abnormal, Blood pressure diastolic increased, Blood pressure increased, Blood pressure systolic abnormal, Blood pressure systolic increased.
Infection	• SOC in Infections and infestations.
Liver Function	• MedDRA (SMQ) Hepatic disorders: Sub-SMQs (Narrow) in Cholestasis and jaundice of hepatic origin; Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions; Hepatitis, non-infectious; Liver related investigations, signs and symptoms (selected relevant). • PTs: Alanine aminotransferase abnormal, Alanine aminotransferase increased, Aspartate aminotransferase abnormal, Aspartate aminotransferase increased, Bilirubin conjugated abnormal, Bilirubin conjugated increased, Blood bilirubin abnormal, Blood bilirubin increased, Blood bilirubin unconjugated increased, Hepatic enzyme abnormal, Hepatic enzyme increased, Hepatic function abnormal, Hyperbilirubinaemia, Hypertransaminasaemia, Liver function test abnormal, Transaminases abnormal, Transaminases increased, Blood alkaline phosphatase abnormal, Blood alkaline phosphatase increased, liver function test increased.
ALT	• PT in Alanine aminotransferase increased.
AST	• PT in Aspartate aminotransferase increased.
Myelosuppression[a]	• MedDRA SMQs (Narrow): Haematopoietic cytopenias affecting more than one type of blood cell, Haematopoietic erythropenia, Haematopoietic leukopenia, Haematopoietic thrombocytopenia. • PTs in Bone marrow toxicity, Haematocrit decreased, Haemoglobin decreased, Haematotoxicity, Anaemia.
Rash	• HLTs in Rashes, eruptions and exanthems NEC; Erythemas; Acnes; Dermatitis and eczema.
Renal	• HLT in Renal failure and impairment. • PTs in Blood creatinine abnormal, Blood creatinine increased, Creatinine renal clearance abnormal, Creatinine renal clearance decreased, Glomerular filtration rate abnormal, Glomerular filtration rate decreased.

AE Category	AE Criteria
Vascular	• HLGTs in Coronary artery disorders; Arteriosclerosis, stenosis, vascular insufficiency and necrosis; Embolism and thrombosis. • HLTs in Arterial therapeutic procedures (excl aortic), Central nervous system haemorrhages and cerebrovascular accidents, Central nervous system vascular disorders NEC, Non-site specific vascular disorders NEC, Peripheral vascular disorders NEC (excluding the 2 PTs Flushing and Hot flush), Transient cerebrovascular events, Vascular imaging procedures NEC, Vascular therapeutic procedures NEC.

a. The following MedDRA PTs will be used for cytopenias: anemia (Anaemia), thrombocytopenia (Thrombocytopenia, Acquired amegakaryocytic thrombocytopenia), neutropenia (Cyclic neutropenia, Febrile neutropenia, Idiopathic neutropenia, Neutropenia).

Abbreviations: HLT=high level term; HLGT=high level group term; MedDRA=medical dictionary for regulatory activities; NEC=not elsewhere classified; PT=preferred term; SMQ=standard MedDRA query; SOC=system organ class.

Appendix 3. Criteria for Potentially Clinically Important Changes in Vital Signs

Variable	Criteria
Systolic blood pressure	<80 or >210 mmHg
Diastolic blood pressure	<40 or >130 mmHg
Heart rate	<40 or >150 bpm
Temperature	<32°C or >40°C
Body weight	≥10% change from baseline value

Abbreviation: bpm=beats per minute.

Appendix 4. Criteria for Potentially Clinically Important Changes in ECG

ECG Parameter	Criteria
Heart rate	Increase of >15 bpm from baseline value and ≥120 bpm
	Decrease of >15 bpm from baseline value and ≤45 bpm
PR interval	Change of ≥20 msec from baseline value and ≥220 msec
QRS interval	≥120 msec
QTcB interval	>500 msec
	Increase of >60 msec from baseline
QTcF interval	>500 msec
	Increase of >60 msec from baseline
	≤450 msec (Men) or ≤470 msec (Women)
	>450 msec (Men) or >470 msec (Women)
Overall evaluation – center reported	Abnormal clinically significant

Abbreviations: bpm=beats per minute; PR interval=measure of the time between the start of the P wave and the beginning of the QRS complex; QRS=the part of the electrocardiogram comprising the Q, R, and S wave, together representing ventricular depolarization; QTc=corrected QT.