Official Title of Study:

AN OPEN LABEL, RANDOMIZED (2:1) PHASE 2B STUDY OF DASATINIB VS IMATINIB IN PATIENTS WITH CHRONIC PHASE CHRONIC MYELOID LEUKEMIA WHO HAVE NOT ACHIEVED AN OPTIMAL RESPONSE TO 3 MONTHS OF THERAPY WITH 400 MG IMATINIB

NCT Number: NCT01593254

Document Date (Date in which document was last revised): 09-Mar-2018

STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

AN OPEN LABEL, RANDOMIZED (2:1) PHASE 2B STUDY OF DASATINIB VS IMATINIB IN PATIENTS WITH CHRONIC PHASE CHRONIC MYELOID LEUKEMIA WHO HAVE NOT ACHIEVED AN OPTIMAL RESPONSE TO 3 MONTHS OF THERAPY WITH 400 MG IMATINIB

PROTOCOL (S) CA180399

VERSION # 1.0

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2 STUDY DESCRIPTION

2.1 Study Design

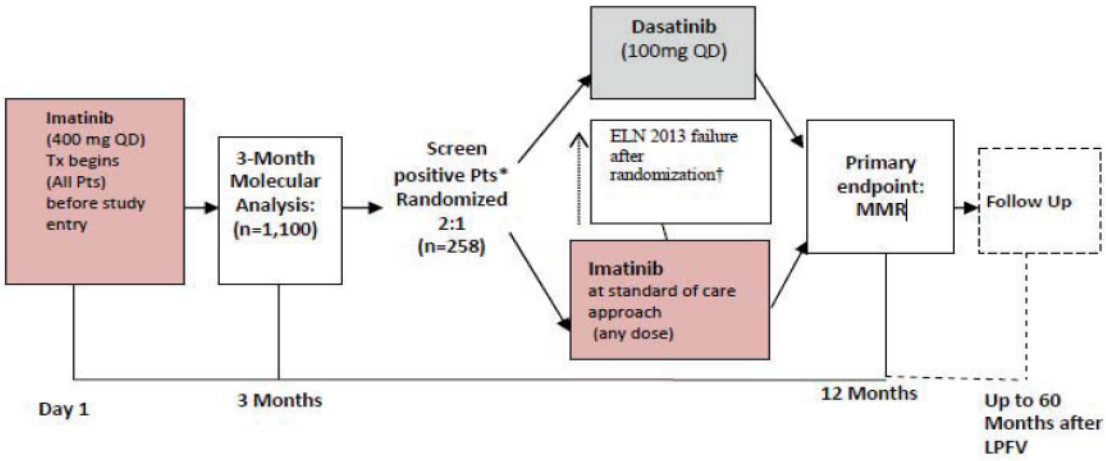
This study is an open-label, randomized, prospective, multi-center, Phase 2b study conducted in patients with CP-CML who have achieved complete hematologic response (CHR) but who have more than 10% IS BCR-ABL at 3 months after first line treatment with imatinib 400 mg QD. Approximately 1,100 patients will be enrolled for screening into this study. Patients who are screened as eligible for the protocol will be randomized to receive either dasatinib 100 mg QD or imatinib with the option to increase dose following a standard of care approach.

Patients will sign the informed consent form before any screening assessment is conducted. The 3- month molecular sample, part of the screening procedure required to establish eligibility, will be analyzed in the central lab. Patients treated with imatinib preceding the 3-month molecular response assessment are considered the screened population. Screened patients with a transcript level of 10% IS or less after 3 months of imatinib 400 mg treatment are excluded from the study and will be considered screen failures.

The study design schema is presented in

Figure 2.1-1.

Figure 2.1-1: Study Design



Randomization may take place up to a maximum of 8 weeks after the 3-month molecular analysis. Randomization will be stratified by Sokal score (high, intermediate, low, unknown) and time between the 3-month molecular assessment and randomization (≤ 4 weeks, > 4 weeks). During the study, patients randomized to the imatinib treatment group who meet the ELN 2013 criteria of failure (Appendix 2) will be crossed over to the dasatinib treatment group, unless the patients have dasatinib resistant mutations.

Patients will be treated for a maximum of 60 months after randomization of the last patient on the assigned regimen (dasatinib or imatinib), unless disease progression, treatment failure or unacceptable toxicity occurs, the patient withdraws consent, or the study is discontinued by the sponsor. This means that the first randomized patient could be treated on study for up to 84 months or more depending on the actual date of the last patient's first visit (LPFV).

[redacted]

2.3 Blinding and Unblinding

Not applicable. This is an open-label study.

[redacted]

[redacted]

2.5 Data Monitoring Committee

An internal data monitoring committee (IDMC) consisting of senior expert representatives of the Sponsor who are independent from the study team will be established. This committee will include at a minimum two physicians and a statistician. This committee will regularly assess study progress at defined intervals (at least 3 times a year and ad hoc as necessary) and review safety data by arm including all SAEs, grade 3 and 4 AEs and discontinuations and examine critical efficacy endpoints (i.e. MMR, time to MMR, PFS) of the study.

The structure, roles, and responsibilities of the IDMC, as well as the timing of analyses, monitoring guidelines, and content of the reports are detailed in the charter of the IDMC

3 OBJECTIVES

3.1 Primary

The primary objective is to compare the rate of MMR at 12 months after Day 1 initiation of first-line treatment with imatinib, in patients randomized at month 3 to treatment with dasatinib 100mg QD or imatinib at any dose, after less than optimal response to first-line imatinib (BCR-ABL > 10% IS).

3.2 Secondary

The secondary objectives are to compare the following between both treatment arms:

- Time to MMR
- Time to $MR^{4.5}$
- Progression Free Survival (PFS)
- Overall Survival (OS)

[redacted]

4 ENDPOINTS

4.1 Primary Endpoints

The primary endpoint for this study is the proportion of randomized patients who achieve MMR 12 months after the first day (Day 1) of treatment with first-line imatinib (up to 9 months after their randomization date) in patients in each treatment group. Additional details will be specified in section 7.

4.2 Secondary Endpoints

Secondary endpoints include additional examination of time to MMR, time to $MR^{4.5}$, PFS and OS.

4.2.1 Time to MMR and time to $MR^{4.5}$

Time to MMR is defined as the time between the randomization date and the first date that MMR criteria are satisfied. Patients who do not achieve MMR will be censored according to rules that will be detailed in section 7.

Time to $MR^{4.5}$ is defined as the time between the randomization date and first date that the $MR^{4.5}$ criteria are satisfied. Patients who do not achieve $MR^{4.5}$ will be censored according to rules that will be detailed in section 7.

4.2.2 Progression Free Survival (PFS)

PFS is defined as the time from the randomization date to the date of either progression or death due to any cause whichever occurs first. Patient who neither progress nor die will be censored. Additional details and rules will be specified in section 7

4.2.3 Overall Survival (OS)

OS is defined as the time from the randomization date to death date and will include deaths from any cause. Patients who do not die will be censored using the last date of follow-up or end of study date. Additional details and rules will be specified in section 7.

[redacted]

4.3.3 Safety

Safety endpoints will include incidence of AEs, serious AEs, AEs leading to discontinuation, and AEs leading to death as well as marked abnormalities in clinical laboratory tests, vital sign measurements, ECGs, chest x-ray and physical examinations. Safety analysis details will be specified in section 7.

[redacted]

[redacted]

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

Patients will be treated for a maximum of 60 months after randomization of the last patient on the assigned regimen, unless disease progression, treatment failure or unacceptable toxicity occurs, the patient withdraws consent, or the study is discontinued by the sponsor. The study will end 5 years after the last patient's first visit. The study will consist of 3 study periods: screening period, on treatment period, and post treatment study follow-up visits.

The screening period is defined as the date of informed consent until the day prior to randomization. During the screening period, all patients are treated with first-line imatinib 400 mg QD. The 3-month molecular responses assessment is considered as part of the screening procedure. The study index date is the day the patient starts imatinib. All time-points are calculated from Day 1 of first-line treatment with imatinib. Eligible patients will be randomized to receive either dasatinib (100 mg daily) or imatinib at any dose. Randomization may occur up to 8 weeks after the screening molecular analysis.

The on treatment period is defined as the date of randomization until 30 days after discontinuation of dasatinib or imatinib. For patients cross over from imatinib to dasatinib, the on treatment period will include two periods: the date of randomization until the day of discontinuation of imatinib; the date of first dose of dasatinib until 30 days after discontinuation of dasatinib. During the treatment period, data will be collected from patients during clinic visits at the following time points: months 4, 5, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54, 60. Patients who remain on the study after month 60 will be assessed yearly and at study close (60 months after the last patient's first visit). An end of treatment visit is required for all patients. If the yearly assessment has occurred within 3 months of study close, the yearly assessment will be the end of study visit.

Post treatment study follow up visits will be performed for patients who discontinue treatment before the end of the study. Patients will be followed annually (±14 days) to collect progression and overall survival information, until the patient dies, lost to follow-up, or study data collection has ended.

Baseline value will be defined as the value obtained from the last assessment conducted on or prior to the first dose date of randomized treatment (after the 3-month first-line imatinib treatment).

6.2 Treatment Regimens

This study is comprised of two treatment regimens as described in section 2.1. After 3 months of first line treatment with imatinib 400 mg QD eligible patients will be randomized to receive

[redacted]

7.1 General Methods

In the analyses described below (except where noted), counts and percentages will be reported for discrete variables with inclusion of unknown or missing values as a separate category. The mean, SD, median, range (minimum and maximum), and number of non-missing values will be reported for each continuous measure.

All efficacy analyses will be performed using randomized patients excluding site 84 and all comparisons will be made between the two treatment groups as randomized unless noted otherwise. Analysis will be adjusted for the stratification factors including Sokal score categories (high, intermediate, low, unknown) and by time between 3-month molecular assessment and randomization categories (≤ 4 weeks, > 4 weeks) where appropriate.

In the instance of a missing or partial adverse event (AE) date, when the month and year are non-missing, the day will be imputed as the 1st of the month unless the 1st of the month is before the first dose of randomized treatment in which case the start day will be the day of the first dose of randomized treatment. For all non-AE data, in the instance of a missing day in a date that has a non-missing month and year, the day will be imputed as the 15th of the month. For all partial dates, in the case of a missing day and month (the date has only the year), the day and month will be imputed as July 1st, unless that date is prior to the first dose date in which case the first dose date will be used.

The following conversion factors will be used to convert days to months or years: 1 month 30.4375 days and 1 year 365.25 days.

Duration (e.g., time from randomization to first dosing date) will be calculated as last date minus first date plus 1 (duration last first + 1).

All statistical tests will be two-sided. An alpha level of 0.05 will be used to determine statistical significance unless otherwise specified. No imputation of missing longitudinal data will be performed. All statistical analysis will be conducted using SAS software, Version 9.2 (or later) of the SAS System[10].

7.2 Study Conduct

7.2.1 Accrual

The following will be summarized for all enrolled patients:

- Number of patients accrued by investigational site
- Number of patients accrued by month.
- Number of patients accrued by the randomization strata (i.e., Sokal score categories (high, intermediate, low, unknown) and by time between 3-month molecular assessment and randomization (≤ 4 weeks, > 4 weeks).

A by-patient listing of accrual will be produced.

7.2.2 Relevant Protocol Deviations

The relevant protocol deviations will be summarized for all randomized patients. The protocol deviations will be programmatically determined from the clinical database.

A by-patient listing of relevant protocol deviations will be produced along with a by-patient listing of all patients excluded from the primary efficacy analysis.

7.3 Study Population

7.3.1 Patient Disposition

The number of patients enrolled, randomized or not randomized (with the reason for screen failure) will be presented. Those patients who were randomized will be further categorized according to whether the patient received treatment. The number of patients who discontinue treatment along with corresponding reason will be tabulated. The number of patients randomized to imatinib and who experienced treatment failure (with the reason for first-line imatinib treatment failure) will be presented. The number of patients randomized to imatinib and crossing over to dasatinib will also be summarized.

Patient disposition data will also be presented in a by-patient listing.

7.3.2 Demographics and Other Baseline Characteristics

Descriptive statistics will be reported for demographic data and patient characteristics (at screening) for all randomized patients by and across strata. Variables to be summarized include age, sex, and race. Age will be calculated by subtracting the patient's date of birth from his or her screening visit date and dividing this difference by 365.25.

In addition, the baseline Sokal score, time between 3-month molecular assessment and randomization, vital signs (including height and weight) at baseline, ECOG performance status at baseline will be summarized by treatment group.

7.3.3 Medical history

A summary of medical history/current medical conditions will be summarized by system organ class (SOC), coded according the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) for all randomized patients.

A by-patient listing of medical history in the randomized patients will be provided.

7.3.4 Physical examinations

Patients with abnormal baseline physical examination will be tabulated by examination criteria for all randomized patients. A by-patient listing will be provided.

7.4 Extent of Exposure

According to the response and toxicity, dose modifications will follow the standard of care recommendations. Dose interruptions or reductions for dasatinib- or imatinib-related adverse events (possibly, probably or certainly related) are described in APPENDIX 1. For an individual patient, dose interruptions, reductions and treatment discontinuation may be more or less conservative than indicated in APPENDIX 1 based on the clinical judgement of the investigator.

Treatment exposure, dose reductions and interruptions will be summarized as follows by treatment group as treated for all treated patients:

- Average daily dose (mg) and duration (days) of treatment
- Number and percentage of patients with at least 1 dose reduction, number of dose reductions, and reasons for reduction
- Number and percentage of patients with at least 1 dose interruption, number of dose interruptions, and reasons for interruption
- Number and percentage of patients with at least 1 dose escalation, number of dose escalations, and reasons for escalation
- Number and percentage of patients with treatment discontinuation, and reasons for discontinuation

For patients who were randomized and treated in the imatinib treatment group, the above will also be summarized for the following groups:

- Patients who didn't cross over to dasatinib: averge daily dose (mg), duration (days) of treatment, dose reduction and interruptions for imatinib
- Patients who crossed over to dasatinib: average daily dose (mg), duration (days) of treatment, dose reduction and interruptions respectively for imatinib before cross over, and for dasatinib after cross over

A summary of each patient's exposure will be presented in a listing.

7.5 Concomitant medications

A summary of concomitant medications will be presented within each treatment group by therapeutic drug class and generic drug name for the enrolled population.

A by-patient listing of concomitant medications in the randomized patients will be provided.

7.6 Efficacy Analyses

7.6.1 Primary Efficacy Analysis

The primary efficacy analysis is to compare the rate of MMR at 12 months after Day 1 initiation of first-line treatment with imatinib, in patients randomized at month 3 to treatment with dasatinib 100mg QD or imatinib at any dose, after less than optimal response to first-line imatinib (BCR-ABL > 10% IS).

MMR is defined as a 3-log reduction in BCR-ABL transcripts from the standardized baseline, which represents 100% on the international scale, so a 3-log reduction is fixed at 0.1% for MMR.

For the response rate analyses, any patients who fail treatment after randomization will be considered non-responders. Additionally, patients who cross-over to dasatinib after randomization will be considered non-responders at and subsequent to the time of cross-over for any response rate analysis.

Response rates and Clopper-Pearson two-sided 95% confidence intervals will be estimated for each treatment group. Differences in response rates between the treatment groups will be assessed using the Cochran-Mantel-Haenszel (CMH) test stratified by Sokal score categories (high, intermediate, low, and unknown) and time from 3-month molecular analysis to randomization (≤4 weeks vs >4 weeks). A two-sided 95% exact confidence interval for the difference in MMR rate at 12 months will be computed.

The primary analysis will be performed on randomized patients excluding site 84, repeated using all randomized patients and all treated patients as sensitivity analyses.

7.6.2 Secondary Efficacy Analyses

Time to event endpoints including time to MMR, $MR^{4.5}$, PFS, and OS will be estimated for each treatment group at 6, 12, 18, 24, 36, 48 and 60 months using Kaplan-Meier method with the Brookmeyer-Crowley method used in the calculation of the confidence intervals. Time to event endpoints will be compared between the dasatinib group and imatinib group using a two-sided stratified log-rank test with categories from the Sokal score and the time between 3 month molecular assessment and randomization as the stratification factors.

In addition, competing risk methodology will be used to account for patients who die or receive a bone marrow transplant. Cumulative incidence functions for time to MMR, $MR^{4.5}$ adjusted for the competing risk of death or receipt of a bone marrow transplant will be estimated. Fine and Gray[11] method will be used to model the cumulative incidence function by defining the hazard of

the cumulative incidence function, known as the subdistribution hazard, and impose the proportional hazards assumption on the subdistribution hazards. Gray's test[12] will be used to analyze time to MMR, $MR^{4.5}$ to compare between the dasatinib group and imatinib group.

Kaplan-Meier plots will also be presented for time to MMR, $MR^{4.5}$, PFS, and OS.

The above analyses of time to event endpoints will be performed on randomized patients excluding site 84 and repeated for all randomized patients as a sensitivity analysis.

The secondary endpoints will only be considered for comparison between the two treatment groups if the primary endpoint is significant. The secondary endpoints will be analyzed sequentially based on the following order:

1. Time to MMR
2. Time to $MR^{4.5}$
3. PFS
4. OS

Statistical testing will proceed sequentially at α 0.05 for each endpoint as long as the preceding endpoint was statistically significant. Testing will stop as soon as an endpoint is not significant.

7.6.2.1 Time to MMR and $MR^{4.5}$ analysis

Time to MMR is the time between randomization date and first date that MMR criteria are satisfied. Patients who do not achieve MMR will be censored according to rules that are summarized in Table 7.5-1.

Time to $MR^{4.5}$ is defined in the same way as time to MMR with censoring according to rules that are summarized in Table 7.5-1.

$MR^{4.5}$ is defined as a 4.5-log reduction in BCR-ABL transcript from the standardized baseline (0.0032% IS, either detectable disease $\leqslant$ 0.0032% BCR-ABL (IS) or undetectable disease in cDNA (in same volume used for BCR-ABL) with $\geqslant$ 32,000 ABL transcripts.

7.6.2.2 Progression Free Survival (PFS) Analysis

PFS is the time from randomization date to progression date or death date, whichever occurs first. Patients who neither progress nor die will be censored. Additional details and rules are specified in Table 7.5-1.

A recent ELN 2013 publication reaffirmed that progression is defined as transformation to accelerated phase or blast crisis. Any of the following events occurring while a patient is continuously on study therapy would define progression. Patients should be on the maximum tolerated dose (as determined by the investigator) before criteria for progression are considered.

- Criteria for accelerated phase CML are met at any time
    - The presence of $\geqslant$ 15%, but < 30% blasts in the blood or bone marrow

- At least 30% blasts plus promyelocytes in the blood or bone marrow
- At least 20% peripheral basophils
- Thrombocytopenia (fewer than 100,000 platelets/mm3) unrelated to treatment

- Criteria for blast phase CML are met at any time
  - At least 30% blasts in the blood or bone marrow
  - Extramedullary involvement (e.g., chloromas), but not hepatosplenomegaly
- Death from any cause during treatment.

The date of progression is defined as the date when any of the above criteria is first met. Patients meeting any criterion for progression will be removed from protocol therapy. The loss of a previously achieved hematologic or cytogenetic response is considered a treatment failure, not disease progression.

Treatment failure to first-line therapy is defined as:

1. Any of the disease progression parameters above

2. At 3 months: less than complete hematologic response (These patients will not be eligible for randomization) and/or No CyR (Ph+ >95%)

3. At 6 months: BCR-ABL >10% and/or Less than PCyR (Ph+ >35%)

4. At 12 months: BCR-ABL >1% and/or Less than CCyR (Ph+ >0%)

5. At any time during treatment, loss of CHR or CCyR; Confirmed loss of MMR (In two consecutive tests, of which one with a BCR-ABL1 transcripts level ⩾ 1%), BCR-ABL1 kinase domain mutations poorly sensitive to imatinib; newly emerging CCA/Ph+

PFS will be analyzed similarly as OS.

Note: Patients failing imatinib therapy at any time point will be crossed-over to the dasatinib arm unless they harbor dasatinib-resistant mutations.

7.6.2.3 Overall Survival (OS) Analysis

OS is defined as the time from the randomization date to the death date and includes deaths from any cause. Patients who have not died will be censored on the last date they are known to be alive. Additional details and rules are specified in Table 7.5-1.

Table 7.5-1: Censoring Rules for Time to Event Analyses		
Time to Endpoint	**Event/Censoring**	**Event/Censoring Date**
MMR MR4.5	1) Event	The first date that MMR (or MR4.5) criteria are satisfied
	2.1) Censoring	Date of last molecular assessment (if patients don't meet MMR [or MR4.5])
	2.2) Censoring	Visit 1 date (randomization date) (if patient have no post-baseline molecular assessment)
PFS	1.1) Event	Date of progression
	1.2) Event	Date of death (if patients die without progression)
	2.1) Censoring	Date of last molecular assessment (if patients have no progression and no death)
	2.2) Censoring	Visit 1 date (randomization date) (if patient has no post-baseline progression assessment and no death reported)
OS	1) Event	Date of Death
	2) Censoring	Date of last known alive (if patients have no death reported)

A sensitivity analysis of Time to MMR, Time to MR4.5, PFS and OS will be performed on the randomized patients excluding site 84. For patients who are crossed over to dasatinib after treatment failure on imatinib, they will be censored at the date of crossover, if they haven't experienced events prior to the date of crossover. If sufficient data exist, the effect of patients crossing over treatments on time to MMR, $MR^{4.5}$, PFS, and OS will be explored using a Cox proportional hazards model with switch in treatment as a dichotomous, time-dependent (i.e., interaction with time to switch to dasatinib), covariate. Time to switch to dasatinib (months) will be calculated as (The crossover date - The randomization date +1) / 30.4375.

[redacted]

[redacted]

7.6.3.2 Molecular and Cytogenetic Response

Molecular Response

To assess the molecular response over time, MMR, $MR^{4.5}$ and MR^{4} response rates will be assessed at 6, 12 ($MR^{4.5}$ and MR^{4} only since MMR at 12 months is primary endpoint), 15, 18, 24, 36, and 48 months for the randomized patients excluding site 84. MMR, $MR^{4.5}$ or MR^{4} response rate is the proportion of randomized patients who achieve MMR, $MR^{4.5}$ or MR^{4} at each time point from Day 1 treatment with first-line imatinib. Response rates at each time point and associated Clopper-Pearson two-sided 95% confidence intervals will be estimated for each treatment group. For the response rate analyses, any patients who fail treatment after randomization and are crossed over or discontinued from the study will be considered non-responders. Difference in response rates at each time point between two treatment groups will be assessed using the CMH test, controlling for Sokal score (high, intermediate, low, and unknown) and the time between the 3-month molecular assessment and randomization ($\leq$ 4 weeks vs >4 weeks).

MR^{4} is defined as a 4-log reduction in BCR-ABL transcript from the standardized baseline (either detectable disease $\leq$ 0.01% BCR-ABL (IS) or undetectable disease in cDNA (in same volume used for BCR-ABL) with $\geqslant$ 10,000 ABL transcripts.

Cytogenetic Response

To assess the cytogenetic response over time, complete cytogenetic response (CCyR) and major cytogenetic response (MCyR) will be assessed at 6, 12, and 18 months for the randomized patients excluding site 84. The rate of CCyR and MCyR is defined as the proportion of randomized patients who achieved CCyR or MCyR at each time-point from Day 1 treatment with first-line imatinib. The response rates at each time point will be analyzed using the same method for molecular responses at each time point.

Cytogenetic Response: cytogenetic response is based on the prevalence of Ph+ cells in metaphase from BM sample.

The criteria for evaluation of CyR are based on the percentage of Ph+ cells in metaphase and are specifically categorized as follows:

CCyR	-> 0%
Partial cytogenetic response (PCyR)	-> 1-35%
MCyR	-> 0-35% (CCyR plus PCyR)
Minor cytogenetic response	-> 36 to 65%
Minimal cytogenetic response	-> 66 to 95%
No cytogenetic response	-> 96 to 100%

If Ph+ cells in metaphase from BM sample data using conventional cytogenetic assessment are not available, fluorescence in situ hybridization (or FISH [peripheral blood]) method is allowed as a substitute. Previous research has shown that these data are highly correlated[2]. The same categorizations will be applied.

Benefit of Early Switch

The benefit, evaluated by response rates and survival, of early switch to dasatinib (at 3 month) over switch at time of imatinib failure (based on ELN 2013 Criteria of failure) later on in the randomized patients will be summarized. Response rates MMR, $MR^{4.5}$, MR^{4}, CCyR, and MCyR, PFS and OS for patients who crossed over are defined similarly as for the patients who did not crossover in the primary and secondary analyses. The patients are categorized into three groups for this analysis: randomized to dasatinib; randomized to imatinib and crossed over to dasatinib later; randomized to imatinib and no crossover. Response rates over time and Clopper-Pearson two-sided 95% confidence intervals will be estimated for each of the three groups. Kaplan-Meier and Brookmeyer-Crowley methods will be used for analysis of PFS and OS for each of the three groups.

In order to further investigate the relationship with the time to switch to dasatinib, log reduction in BCR-ABL will be summarized by three treatment groups above at 6, 12, 24, 36, 48 and 60 months since randomization to explore if there are any trends or patterns among the subjects in the three groups.

Medication Compliance

To explore the correlation of medication compliance (treatment adherence) with disease response, medication compliance (treatment adherence) will be assessed using MMAS-8. The MMAS-8 is a validated self-reported measure of medication adherence. The scale is a commonly used adherence tool composed of yes/no questions about past medication use that is simple to use. Each item measures a specific medication-taking behavior. Response categories are yes/no for each item with a dichotomous response and a 5-point Likert response for the last item. Patients with higher scores are predicted to be more adherent to prescribed therapies, while patients with lower scores are at greater risk for non-adherent behavior. Descriptive statistics of patient MMAS-8 scores will be presented at each study visit for each treatment group for the randomized patients. Analysis of response rates of primary and secondary clinical endpoints ($MR^{4.5}$ and MR^{4}) will be stratified by level of patient adherence (MMAS-8 score), if there are at least 10 patients in each category for each treatment group. Patient adherence will also be incorporated into time-to-event analysis for MMR and $MR^{4.5}$ by including MMAS-8 score, along with treatment group, Sokal score (high, intermediate, low, and unknown), the time between 3-month molecular measurement to randomization ($\leqslant$ 4 weeks, $>$ 4 weeks) in proportional hazards models of these endpoints.

7.7 Safety Analyses

Safety assessments will include incidence of AEs, serious AEs, AEs leading to discontinuation, as well as marked abnormalities in clinical laboratory tests, chest x-ray, pregnancy test for women of child-bearing potential, vital sign measurements, ECGs, and physical examinations.

Descriptive statistics (counts and percents) will be provided for all treated patients (regardless of crossover status) by treatment group using as treated treatment information, as well as for patients who crossed over from imatinib to dasatinib and were treated with dasatinib.

7.7.1 Adverse Events

AEs will be coded according to the latest version of MedDRA. The intensity of AEs will be graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0.

AEs occurring on or after Day 1 of receiving randomized treatment and no later than 30 days following the last day of treatment will be considered treatment emergent. In the absence of evidence of discontinuation of therapy, patients are assumed to be still on-study.

For patients crossing over from imatinib to dasatinib during the study, the actual (as treated) treatment will be determined based on the cross over date and AE starting date. Treatment emergent AEs for patients who cross over to dasatinib are defined as those AEs that occur after the first dose date of dasatinib and no later than 30 days following the last day of treatment.

Treatment-related AEs, defined as an adverse event which was determined to be related by physician, will be summarized. If a patient experiences multiple occurrences of the same AE with different relationship to study medication categories, the patient will be counted once as treatment-related. In the event has the relationship to study drug as missing, the relationship to study drug will be taken as "related" in all relevant statistical analyses.

The intensity of AEs will be graded 1 to 5. If a patient experiences the same AE more than once with different toxicity grade, then the event with the highest grade will be tabulated in "by grade" tables. In addition, AEs with missing intensity will be presented in the summary table as an intensity category of "Missing."

AEs of special interest in this study include:

- Musculoeskeletal disorders
- Connective tissue disorders
- Vascular disorders

Tables summarizing the number of patients experiencing AEs and patient incidence for AEs will be generated for each of the following summaries by treatment group regardless of crossover as well as for patients who crossed over from imitinab to dasatinib and were treated with dasatinib:

- Overall summary of AEs
- AEs presented by MedDRA system organ class and preferred term
- All AEs by worst CTCAE grade category

- Treatment-related AEs presented by MedDRA system organ class and preferred term
- Treatment-related AEs by worst CTCAE grade category
- Serious AEs presented by MedDRA system organ class and preferred term
- Treatment-related serious AEs by MedDRA system organ class and preferred term
- AEs leading to study discontinuation
- AEs with fatal outcome.
- AEs of special interest by worst CTCAE grade category
- Treatment-related AE's of special interest by worst CTCAE grade category

Adverse events due to intolerance of study treatment will also be summarized. Intolerance of treatment is defined as recurrent ≥Grade 3 hematologic toxicity or ≥Grade 2 non-hematologic toxicity despite dose reduction necessitating discontinuation of protocol therapy.

The above summaries will be generated by treatment group regardless of crossover as well as for patients who crossed over from imatinib to dasatinib and were treated with dasatinib.

Toxicity rates, using the worst CTCAE Grade per patient, for selected Grade 3 treatment-related adverse events (fluid retention, pleural/pericardial effusion, CHF, cardiac dysfunction, rash, neutropenia, thrombocytopenia, anemia, leucopenia, AST, ALT, total bilirubin and dose reduction/interruption due to toxicity) will be compared between the two treatment groups using the Fisher exact test.

In addition, each unique AE will be summarized by treatment group with number of events (i.e., 0 event, 1 event, 2-3 events, > 4 events).

Corresponding by-patient data listings for all adverse events, adverse events leading to discontinuation, and adverse events with fatal outcome will be provided for the randomized patients.

A by-patient data listing for all serious adverse events will be provided for the enrolled patients.

The summary tables and listings will reflect the actual treatment for the safety analysis unless specified otherwise.

7.7.2 Death

A listing and a table will be provided to summarize all deaths and deaths within 30 days after the date of last dose.

7.7.3 Clinical Laboratory Evaluations

Clinical laboratory values from the laboratory tests will be graded according to NCI CTCAE, Version 4.0 for applicable tests. Normal ranges will be used to determine the categories of High, Low, and Normal for lab tests that have no severity grade, if available.

A listing of patients with laboratory abnormalities will be provided.

7.7.3.1 Hematology

The worst NCI CTCAE grade for white blood cell (WBC) counts, absolute neutrophil counts (ANC), absolute lymphocyte counts, platelet counts, and hemoglobin during the treatment period will be summarized for all treated patients by treatment group as well as for patients who cross over to dasatinib and treated with dasatinib.

Hematology lab results and changes from baseline by visit during the treatment period will be summarized.

7.7.3.2 Serum Chemistry

The worst NCI CTCAE grade for AST (SGOT), ALT (SGPT), alkaline phosphatase (ALP), total bilirubin, serum creatinine, Na, K, Mg, and P will be summarized during the treatment period will be summarized for all treated patients by treatment group as well as for patients who cross over to dasatinib and treated with dasatinib.

Serum chemistry lab results and changes from baseline by visit during the treatment period will be summarized.

7.7.4 Electrocardiograms, Echocardiograms and Chest X-rays

The 12-lead ECG to determine baseline QT interval corrected (QTc) will be documented at baseline and as clinically indicated. Echocardiogram and chest x-ray measurements will be documented at baseline and as clinically indicated.

Electrocardiograms (ECGs), echocardiogram, and chest x-ray measurements will be summarized by visit during the treatment period for all treated patients by treatment group as well as for patients who cross over from imitinab to dasatinib.

In addition, the ECG analysis will report the frequency distributions of maximal QTc intervals (Fridericia) and the changes from baseline.

Corresponding by-patient listings for ECGs, echocardiogram, and chest x-rays will be provided

7.7.5 Vital Signs

Vital sign measurements (systolic blood pressure (BP), diastolic BP, heart rate, and temperature) will be summarized by visit during the treatment period for all treated patients by treatment group (regardless of crossover) as well as for patients who crossed over from imitinab to dasatinib.

A by-patient listing of vital sign measurements will be provided.

7.7.6 Physical Examination

Physical examination parameters will be summarized by visit during the treatment period for all treated patients by treatment group as well as for patients who cross over to dasatinib and treated with dasatinib.

All physical examination abnormal findings will be listed.

7.7.7 Pregnancy

A by-patient listing of pregnancy test results will be provided.

7.7.8 ECOG Performance Score

Eastern Cooperative Oncology Group (ECOG) performance status score will be collected at baseline and during the treatment period. ECOG performance score will be summarized by visit during the treatment for all treated patients by treatment group as well as for patients who cross over to dasatinib and treated with dasatinib.

Post-baseline ECOG performance score cross-tabulated by worst (highest) score with the score (0, 1 or 2) at baseline (shift table) may be also be needed.

7.8 Pharmacokinetics

Not applicable.

7.9 Biomarker Analyses

Not applicable.

7.10 Interim Analyses

The primary analysis will be based on the Month 12 evaluation although descriptive summaries will be produced through the conclusion of all patients' participation in the trial.

An interim analysis is planned when all 258 patients have been followed until Month 12 (calculated from day 1 of initiation of first line imatinib. i.e., at the time of the primary endpoint final analysis). This analysis will assess the secondary efficacy endpoints as well as safety endpoints. At yearly interim looks (year 1, year 2, year 3, year 4), the four secondary efficacy endpoints will be tested sequentially at an alpha level of 0.0001. At the final analysis (year 5), the four secondary efficacy endpoints will be tested sequentially at an alpha level of 0.0496. Secondary endpoints are sequentially ranked as follows:

1. Time to MMR
2. Time to MR[4,5]
3. PFS
4. OS

8 CONVENTIONS

Unless specified otherwise, the following conventions may be used for imputing partial dates for analyses requiring dates:

- If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
- If both the day and the month are missing, "July 1" will be used to replace the missing information.
- If a date is completely missing, it will be considered as missing.

For adverse events:

- If only the day of the month is missing, the first day of the month will be used to replace the missing day unless the 1st of the month is before the first dose of study treatment. In that case the start day will be the day of the first dose of treatment.
- If both the day and the month are missing, "January 1" will be used to replace the missing information unless January 1 is before the first dose of study treatment. In that case the start day and month will be the day and month of the first dose of treatment.
- If a date is completely missing, it will be considered as missing.

For death dates, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day. The imputed date will be compared to the last known date alive + 1 day and the maximum will be considered as the death date.
- If the month or the year is missing, the death date will be imputed as the last known date alive + 1 day.
- If the date is completely missing but the reason for death is present the death date will be imputed as the last known date alive + 1 day

The following conversion factors will be used to convert days to months or years: 1 month 30.4375 days and 1 year 365.25 days.

Duration will be calculated as follows: Duration (Last date - first date + 1)

Last known date alive will be defined based on all appropriate dates collected on the CRF.

All statistical analyses will be carried out using SAS (Statistical Analysis System software, SAS Institute, North Carolina, USA) unless otherwise noted.

9 CONTENT OF REPORTS

All analyses described in this SAP will be included in the Clinical Study Report(s) except where otherwise noted. Refer to the Data Presentation Plan for mock-ups of all tables and listings.