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Open-Label Single Arm Phase 2 Study Evaluating Dasatinib Therapy Discontinuation In Patients
With Chronic Phase Chronic Myeloid Leukemia (CP-CML) With Stable Complete Molecular
Response (CMR) DASFREE

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**STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT**

**OPEN-LABEL SINGLE ARM PHASE 2 STUDY EVALUATING DASATINIB THERAPY
DISCONTINUATION IN PATIENTS WITH CHRONIC PHASE CHRONIC MYELOID
LEUKEMIA (CP-CML) WITH STABLE COMPLETE MOLECULAR RESPONSE (CMR)
DASFREE**

PROTOCOL(S) CA180406

VERSION # 3.1

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Schedule of Analyses:

The primary analysis will be performed when the primary endpoint, MMR status at 12 months after dasatinib discontinuation is available to be evaluated for all the enrolled subjects.

In addition to primary analysis, an interim analysis is planned when 30 patients have been followed for 12 months after discontinuation of dasatinib. This analysis will assess specific safety and efficacy endpoints and will be detailed in the statistical analysis plan.

Regular reviews of safety and efficacy data listings and pharmacovigilance reports will be performed. These reviews will be conducted by an internal data monitoring committee (IDMC) made up of representatives who are independent from the study team. The structure, roles, and responsibilities of the IDMC, as well as the timing of analyses, monitoring guidelines, and content of the reports will be detailed in the charter of the IDMC.

This regular review will be repeated at 6 months intervals until the final analysis is conducted when all patients have been followed for 5 years.

2 STUDY DESCRIPTION

2.1 Study Design

This is an open-label, single-arm study in adult patients with CP-CML who have received dasatinib treatment for a minimum of 2 years at the time of enrollment and have confirmed dasatinib-induced complete molecular remission (defined as ≥ 4.5 -log reduction of BCR-ABL transcript as determined by local standards) ongoing for at least 1 year immediately prior to study enrollment.

Prospective patients will be prescreened to confirm dasatinib-induced CMR stable for a minimum of nine months. CMR must be documented by at least three assessments, 2-6.5 months apart conducted at a local lab. Once stable CMR is confirmed at prescreening, patients are eligible for the study sponsored molecular analyses conducted via the central lab. If the first study sponsored molecular analysis assessment confirms CMR, the assessment will be repeated after three months. Patients are eligible for enrollment if both assessments from the central lab confirm CMR (MR4.5).

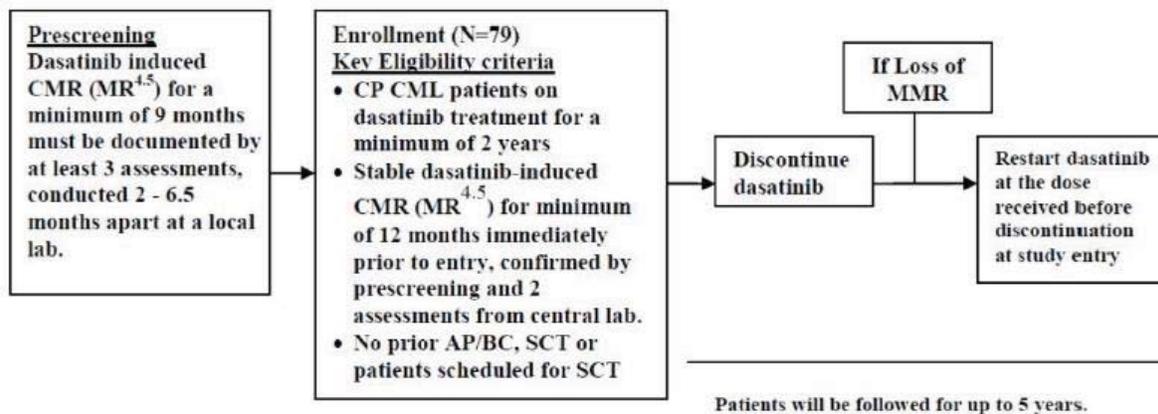
Once all eligibility criteria are met, patients will be enrolled and dasatinib will be discontinued.

Patients will be monitored for maintenance of MMR (BCR-ABL transcripts $< 0.1\%$ IS). In case of loss of MMR, dasatinib treatment will be resumed at the dose level the patient was receiving before dasatinib was discontinued at study entry. Patients who have restarted treatment due to loss of MMR will remain on treatment for the duration of the study. Dose escalations and adjustments in case of toxicities are permitted as described in Section.4.3.1 (Dose Adjustments) of the protocol.

A rise of PCR $> 0.0032\%$ (4.5 log reduction) on international scale (IS) after discontinuation of dasatinib should not trigger dasatinib re-initiation, if the BCR-ABL transcripts remain below 0.1% on IS. All patients on study will be followed for 5 years after enrollment. The study will end 5 years after the first visit of the last enrolled patient.

The study design schematic is presented in [Figure 2.1-1](#).

Figure 2.1-1: Study Design Schematic



AP/BC =accelerated phase/blast crisis; CMR = complete molecular response.
IS = International Scale; SCT = stem cell transplant; Month = 30 days

CMR (MR^{4.5}) defined as $\leq 0.0032\%$ (IS) or ≥ 4.5 log reduction of BCR-ABL transcript as determined by local standards

2.2 Treatment Assignment

This is an open-label, single arm study. Patients will be identified according to the standard trial procedure of each site.

Study drugs include Investigational Medicinal Products (IMP) and can consist of the following:

All products, active or placebo, being tested or used as a comparator in a clinical trial. See Table 2.2-1 for product description.

Table 2.2-1: Product Descriptions

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Dasatinib	20 mg, 50 mg, 80 mg, 100 mg, and 140 mg	Various packaging configurations Open label	Not applicable	White to off-white, biconvex, film-coated tablets	Refer to label on container or package insert/summary of product characteristics

2.3 Blinding and Unblinding

Not applicable.



4 ENDPOINTS

Primary Efficacy Endpoints:

The primary efficacy endpoint is the proportion of patients who maintain MMR at 12 months after dasatinib discontinuation without re-starting dasatinib treatment in the enrolled patients in the study.

Secondary Efficacy Endpoints:

The secondary efficacy endpoints include:

- EFS at 12, 24, 36, 48 and 60 months after dasatinib discontinuation
- RFS at 6, 12, 18, 24 months and every 6 months thereafter after dasatinib discontinuation.
- Assessment of BCR-ABL kinetics for patients who experience loss of CMR but not MMR.
- Assessment of BCR-ABL kinetics in patients in CMR with measurable levels.
- The rate of transformation to AP/BC
- PFS
- OS

Safety endpoints include incidence of AEs, serious AEs, AEs leading to discontinuation, and death as well as marked abnormalities in clinical laboratory tests, vital sign measurements, ECGs, and physical examinations.

Quality of life assessments: EORTC QLQ-C30 and MDASI-CML during discontinuation of study treatment and during treatment (re-start of dasatinib) will be evaluated. Health care utilization during the discontinuation of study treatment and during treatment (re-start of dasatinib) study periods will also be explored and reported separately from the clinical study report.

5 SAMPLE SIZE AND POWER

This is an open-label, single-arm study with no comparative objective.

A 75% MMR rate at 12 months after dasatinib discontinuation is considered clinically relevant. Under such an assumption, a sample size of 74 patients will ensure a 20% width for a 95% confidence interval. To accommodate an expected 5% drop-out rate, a total of 79 patients will be enrolled into this trial.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

All patients in the study will be followed for 5 years after enrollment. The study will end 5 years after the first visit of the last enrolled patient. The study will consist of 3 study periods: on-

treatment during the screening period; off-treatment (upon discontinuation of dasatinib); and on-treatment study periods.

The on-treatment during screening period is defined as the period between the date of informed consent and the day prior to the start date of dasatinib discontinuation. The off-treatment period is defined as the period between the start date of dasatinib discontinuation and the date when a patient start losing MMR, or the last date in the study, whichever occurs first. For patients who restarted dasatinib, the on-treatment after restarting dasatinib is defined as the period between the date dasatinib is restarted and the last date in the study.

The study design schematic is presented in (Figure 2.1-1).

6.2 Treatment Regimens

All enrolled patients will discontinue dasatinib at baseline visit. Patients will be identified according to the standard trial procedure of each site.

6.3 Populations for Analyses

- Enrolled patients: All patients who signed an informed consent and meet study eligibility criteria and are discontinued from dasatinib.
- Evaluable patients: All enrolled subjects who have at least one BCR-ABL assessment.

All enrolled patients will be used in the tabulation of subject disposition and will be used in the analysis of baseline characteristics and efficacy. Also, the efficacy endpoints will be analyzed for evaluable subject population. Safety, and health outcome will be tabulated and analyzed for the enrolled patients. Extent of exposure will be summarized in the enrolled patients who restarted dasatinib.

6.4 Subgroups for Analyses

Efficacy will be described for each of the following subgroups:

- Patients in CMR (MR4.5) \leq 24 months prior to dasatinib discontinuation are those patients who achieve a sustained CMR ($\leq 0.0032\%$ (IS) or ≥ 4.5 log reduction of BCR-ABL transcript levels as determined by local standards) for a duration of up to and including 24 months calculated from the date patients achieve CMR for the first time up to the date of baseline visit.
- Patients in CMR (MR4.5) $>$ 24 months prior to dasatinib discontinuation are those patients who achieve a sustained CMR for a duration superior to 24 months calculated from the date patients achieve CMR for the first time up to the date of baseline visit.
- Patients with first versus patients with second or third line of therapy.
- Patients with Dasatinib as second or third line of therapy due to Resistance vs due to Intolerance.

Subgroups of patients with resistance and intolerance to 2nd or 3rd line of therapy (i.e., imatinib, nilotinib, ponatinib or bosutinib) will be defined as follows:

- If patient has "disease progression" or "inadequate response" entered under "Reason for Therapy Action" box in the "Previous and Concomitant Therapies for CML" electronic case report form (eCRF) page this will be counted as resistance;

- It will be counted as intolerance if patient has "side effects", or "Other: side effect", or "hematologic side effect", or "non-hematologic side effect", or "musculoskeletal side effect", or "non-hematologic adverse event" entered under "Reason for Therapy Action" box in the "Previous and Concomitant Therapies for CML" eCRF page.

If an instance of resistance is recorded, no matter if a second event of intolerance is recorded, this patient is considered as a resistant subject.

Subgroups of patients with dasatinib as first line or second/third line treatment will be defined based on the information collected at study entry through the "Previous and Concomitant Therapies for CML" eCRF page.

- Patients with dasatinib as first line treatment are those patients that responded "Yes" to the question "Did subject take previous or current therapies?" and have only dasatinib or Sprycel recorded under "Therapy" will be considered under the subgroup of patients with dasatinib as first line treatment. If the patient has at least one record with Imatinib, or Gleevec, or Glivec, or Tassigna, or Nilotinib or Ponatinib or Bosutinib under "Therapy" then such patient will not be included in the subgroup of patients with dasatinib as first line of treatment.
- Patients with dasatinib as second/third line treatment are those patients that responded "Yes" to the question "Did subject take previous or current therapies?" and have either Imatinib, or Gleevec, or Glivec, or Tassigna, or Nilotinib or Ponatinib or Bosutinib recorded under "Therapy" with a start date and end date of therapy prior to date of study entry (i.e. date informed consent form signed) will be considered under the subgroup of patients with dasatinib as second/third line treatment. Hydrea or Hydroxyurea are not to be considered as prior therapies.

7 STATISTICAL ANALYSES

SAS® Version 9.2 or higher will be used for statistical analyses, tabulations, and graphical presentations.

7.1 General Methods

In the analysis 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.

Summary statistics will consist of the number and percentage of patients in each category for discrete variables, and the sample size, mean, median, standard deviation (SD), minimum and maximum for continuous variables.

All mean and median values will be formatted to one or more decimal place than the measured value. Standard deviation values will be formatted to two or more decimal places than the measured value. Minimum and maximum values will be formatted to the same decimal place as the measured value. All percentages will be rounded to one decimal place. The number and percentages of responses will be presented in the form XX (XX.X), where the percentage is in the parentheses.

All analysis and summary tables will have the analysis population sample size (i.e., number of patients) in the column heading. All listings will be sorted for presentation in order of subject identification and date of procedure or event.

Confidence intervals (CIs) will be presented as 2-sided 95% CIs unless specified differently for a given analysis.

Baseline value will be defined as the last assessment conducted on or prior to visit 1 (baseline visit).

7.2 Analysis Visits

For binary outcome of molecular response, study visits will be analyzed on the basis of the events schedule specified in the study protocol (Section 5.1), allowing a little variance in actual practice. Subjects who remained MMR up to 12 months need to keep BCR-ABL transcripts < 0.1% IS for at least 345 days. The detail for each analysis visit is specified in Table 7.2-1

Table 7.2-1: Analysis of Study Visits for Molecular Response

Nominal Visits	Target Day from Off Treatment	Remains MMR up to Nominal Visit
6 Months	165 days	>= 160 days
12 Months	350 days	>= 345 days
24 Months	730 days	>= 715 days
36 Months	1095 days	>= 1080 days
48 Months	1460 days	>= 1445 days
60 Months	1825 days	>= 1810 days

Subjects who remained MR4.5 will be analyzed in the same method.

Safety endpoints and patients reported outcomes (PRO) are evaluated in either 3 months or 6 months interval. They will be analyzed by analysis visits based on the events schedule specified in the study protocol (Section 5.1). Please note that if subjects' measurements were done just 1 day later than the dasatinib discontinuation date, it will be still included in defining baseline. The detail of each analysis visit is specified in Table 7.2-2

Table 7.2-2: Analysis of Study Visits for Safety Endpoints and PRO

Nominal Visits	Target Day from Off Treatment	Analysis Visit Window
Baseline	On or prior to dasatinib discontinuation	<= start day of dasatinib discontinuation +1
3 Months	90 days	3 – 100 days
6 Months	180 days	101 – 190 days
9 Months	270 days	191 – 280 days

Table 7.2-2: Analysis of Study Visits for Safety Endpoints and PRO

Nominal Visits	Target Day from Off Treatment	Analysis Visit Window
Every 3 Months thereafter	Months*30 days	$((\text{Months} - 3) * 30 + 11)$ – (Month*30 + 10) days
Restart Baseline	On or prior to restarting dasatinib	\leq restart day
3 Months after restarting dasatinib	90 days since restarting dasatinib	(Restart day + 1) – (Restart day + 99) days
6 Months after restarting dasatinib	180 days since restarting dasatinib	(Restart day + 100) – (Restart day + 189) days
9 Months after restarting dasatinib	270 days since restarting dasatinib	(Restart day + 190) – (Restart day + 279) days
Every 3 Months thereafter	(Restart Visit Number – 1)*90 days since restarting dasatinib	$((\text{Restart Visit Number} - 2) * 90 + 11) -$ $(\text{Restart Visit Number} - 1) * 90 + 10)$ days

If more than one result for a parameter is obtained in an analysis visit window, the result with the data closest to the target day of the scheduled visit will be used. In the event of 2 observations equidistant to the target day, the later of the observations will be used. In case there are two observations collected at the same day, the worse value will be used.

7.3 Study Conduct

All patients with any relevant protocol deviations or violations will be identified. All protocol deviations will be listed and summarized in the study report. The relevant protocol deviations are listed in [Section 7.4.2](#) below.

7.4 Study Population

7.4.1 Subject Disposition

The total number of patients enrolled into the study will be presented. The screen failures and reasons for screen failures will be summarized by frequency and percentage of the total number of subjects screened.

The number and percentage of patients who restarted treatment, reasons for restarting treatment, and patients who discontinued study drug after restarting treatment will be presented for the on-

treatment study period and total number of patients enrolled into the study. Reasons for restarting treatment will be summarized for all patients with the following categories:

- Failure to maintain MMR levels of BCR-ABL lower than 0.1% on IS
- Loss of CHR
- Loss of CCyR
- Other

The number and percentage of patients who discontinued the study will be summarized during off-treatment period (upon discontinuation of dasatinib), the on-treatment period, and total number of patients enrolled into the study. Reasons for discontinuation from the study will be summarized for all patients with the following categories:

- Disease progression
- Adverse Events (AEs) related to study drug
- Death
- AE unrelated to study drug
- Subject request to discontinue treatment
- Subject withdrew consent
- Lost to follow-up
- Maximum clinical benefit
- Poor/non-compliance
- Subject no longer meets study criteria
- Administrative reason by Sponsor
- Other

Finally, summary statistics for the distribution of time after dasatinib discontinuation will be presented for the total number of patients enrolled, subjects that reached at least 6 and 12 months after discontinuation of dasatinib. Number of patients enrolled will also be presented for each site.

A by-patient listing of study disposition in the enrolled population will be provided.

7.4.2 Protocol Deviations

Each patient's data will be examined for protocol deviations. The relevant protocol deviations will be summarized for the enrolled population. Relevant protocol deviations will be programmatically determined from the clinical database. The following relevant protocol deviations will be summarized:

- Violation of inclusion criteria (only 2.a and 2.b)
- Violation of exclusion criteria (only 1.b, 1.c, and 1.e)
- Molecular labs never done
- Molecular labs done late
- No treatment restart after loss of MMR

A by-patient listing of patients with all protocol deviations will be provided.

The inclusion and exclusion criteria are described in Sections 3.3.1 and 3.3.2., respectively, in the protocol.

7.4.3 Demographic and Baseline Characteristics

The demographic and baseline characteristics will be summarized for the enrolled population.

The following demographic and baseline characteristics will be summarized:

- Age (years)
- Gender
- Race
- Performance status (Eastern Cooperative Oncology Group - ECOG)
- Prior Interferon- α (IFN)
- Sokal
- Time from diagnosis to dasatinib discontinuation
- Time in MR 4.5 before dasatinib discontinuation
- Last Dose of Dasatinib received prior to discontinuation

The above demographic and baseline characteristics will also be summarized separately for those patients who lose MMR and patients who do not lose MMR.

Finally, the number and percentage of treatment restart status in patients with the loss of MMR will be summarized. A detailed summary of treatment restart status will be reported to include the number of patients with loss of MMR, the number of patients who restart along with reasons and did not restart treatment along with reasons, number of patients who restarted treatment and regained MMR/CMR(MR4.5) (separately), and time to regain MMR/CMR(MR4.5) (separately), and number patients who restarted treatment and did not regain MMR, and time from restart date to latest visit date (≤ 6 months, > 6 months). For those patients who restarted dasatinib treatment and regained MMR/CMR(MR4.5), time to regain MMR/CMR(MR4.5) will be calculated as follows:

- Time to regain MMR(months) = $[(\text{date regained MMR} - \text{date restarted dasatinib treatment}) + 1] / 30.4375$
- Time to regain CMR(MR4.5) (months) = $[(\text{date regained CMR(MR4.5)} - \text{date restarted dasatinib treatment}) + 1] / 30.4375$

The reasons for restarting/not restarting treatment will be taken from the dasatinib treatment restart status page of the CRF.

7.5 Medical History

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

A by-patient listing of medical history in the enrolled population will be provided.

7.6 Extent of Exposure

Dasatinib dose adjustments are allowed during the restart of treatment with the study drug for patients losing MMR. In the case of loss of MMR during the off treatment period, dasatinib treatment will be resumed at the dose the patient received before dasatinib was discontinued at study enrollment. Dose adjustments for response and toxicity are presented in Table 4.3.1 of the protocol.

Dose reduction is defined as when the dose assigned after restarting dasatinib is at a lower dose level than the assigned dose at the previous visit.

Dose interruption is defined as omission of dosing on at least 2 consecutive study days during the on-treatment study periods. If a patient does not resume dosing, then this will not be considered a dose interruption and will be considered a treatment discontinuation.

Treatment discontinuation is defined as when a patient discontinues dasatinib after restarting dasatinib due to loss of MMR.

Dose interruptions or reductions for dasatinib related AEs occurring on study during the on-treatment periods are described in [APPENDIX 1](#).

Treatment exposure and dose reductions and interruptions will be summarized as follows during the on-treatment study period (patients who restart dasatinib):

- Number of doses administered and duration (months) of exposure
- Number and percentage of patients with at least 1 dose reduction, number of dose reductions, and reasons (adverse event or other) for reduction
- Number and percentage of patients with at least 1 dose interruption, number of dose interruptions
- Number and percentage of patients with a treatment discontinuation

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

7.6.1 Concomitant Medications

Medications reported on the Concomitant medications CRF pages will be code to therapeutic drug classes and generic drug names using the latest version of the WHO drug dictionary.

Concomitant medications are defined as medications that were either initiated before enrollment during the screening period, or initiated during the restart of dasatinib when the study drug will be administered until the end of the study.

A summary showing the number and percentage of patients who took concomitant medications will be presented by therapeutic drug class and generic drug name for the enrolled population.

A by-patient listing of concomitant medications will be provided.

7.7 Efficacy

This section describes the efficacy analyses for the study. No formal statistical testing will be performed. Summary statistics will be provided for efficacy data using the enrolled subject population. The efficacy endpoints will also be analyzed for the evaluable subject population.

Screening/baseline, off-treatment (Dasatinib discontinued), and on-treatment (Dasatinib restart) assessments for the determination of efficacy include complete blood count (CBC) with differential and platelet (PLT) count, cytogenetics (if clinically indicated), and molecular analysis (qualitative polymerase chain reaction [Q-PCR]). Samples for mutational analysis will be drawn at baseline (and stored for future exploratory analysis), and at the time of loss of MMR or any response failure after reinitiating dasatinib as determined by other planned assessments, and as specified in the time and events schedule.

Efficacy endpoints will be based on molecular (Q-PCR performed in a centralized lab and expressed in IS) assessments done throughout the study at the time points specified in the flow chart/time and events schedule presented in [APPENDIX 3](#). Other relevant complementary efficacy endpoints will be based on hematologic and cytogenetic response.

The following definitions are to be taken into account for the efficacy analyses:

Hematologic Response - a complete hematologic response (CHR) is obtained when all the following criteria are met in peripheral blood (PB) sampling:

- WBC $\leq 10,000/\text{mm}^3$
- Platelets $< 450,000/\text{mm}^3$
- Peripheral blood basophils $< 5\%$
- No blasts or promyelocytes in peripheral blood
- $< 5\%$ myelocytes plus metamyelocytes in peripheral blood
- No extramedullary involvement (including no hepatomegaly or splenomegaly).

If a subject failed on any of criteria above on or after progression, he would be considered as loss of CHR.

Cytogenetic response (CyR) - is based on the prevalence of Ph⁺ cells in metaphase from bone marrow (BM) sample. The criteria for evaluation of CyR are based on the percentage of Ph⁺ cells in metaphase and are specifically categorized as follows (with ideally 25 metaphases, but at least 20 metaphases from a BM sample evaluated ⁵):

- Complete Cytogenetic Response (CCyR): 0% Ph⁺ cells in metaphase in BM
- Partial Cytogenetic Response (PCyR): 1 to 35% Ph⁺ cells in metaphase in BM⁵
- Minor CyR: 36 to 65% Ph⁺ cells in metaphase in BM
- Minimal CyR: 66 to 95% Ph⁺ cells in metaphase in BM
- No CyR: 96 to 100% Ph⁺ cells in metaphase in BM
- Major Cytogenetic Response (MCyR) is defined as CCyR plus PCyR.

For the assessment of CCyR, if Ph⁺ cells in metaphase from the BM sample data using conventional cytogenetic assessment are not available, fluorescence in situ hybridization (FISH) of blood interphase cell nuclei can substitute for bone marrow cell metaphases. The same categorizations will be applied, except CCyR according to FISH will be defined by $< 1\%$ BCR-ABL1–positive nuclei of at least 200 nuclei.^{6 7 8}

Molecular response (MR) - will be assessed using BCR-ABL transcript levels measurement by real-time quantitative polymerase chain reaction (Q-PCR performed in a centralized lab and expressed in IS).

- MMR is defined as BCR-ABL transcripts $< 0.1\%$ IS⁶.
- CMR is defined as $\leq 0.0032\%$ or ≥ 4.5 log reduction of BCR-ABL transcript levels MR^{4,5}.
- The rate of MMR is defined as the proportion of subjects who maintain MMR at 12, 24, 36, 48 and 60 months after dasatinib discontinuation, without restarting dasatinib at study entry. Also, the MMR rate will be estimated for the evaluable patients.

Event-free survival (EFS) - is defined as the time from the date of dasatinib treatment discontinuation to date of loss of MMR.

The rate of EFS at 12, 24, 36, 48 and 60 months will be estimated from the Kaplan-Meier (KM) curve.

Relapse (during off-treatment period) - is defined as any of the following events while a subject is on study:

- loss of MMR,
- loss of CCyR,
- loss of CHR,
- or progression to advanced/blastic phase.

Relapse-free survival (RFS) is defined as the time from dasatinib treatment discontinuation to the date of relapse. RFS rate will be estimated from the KM curve at 6, 12, 18, and 24 months and every 6 months thereafter. Subjects who do not relapse will be censored on the date of their last molecular assessment.

Progression – is defined by any of the following events occurring while a subject is in the study:^{6,9}

- Accelerated Phase (AP):
 - Blasts in PB or BM 15–29%;
 - Blast + promyelocytes $\geq 30\%$ with blasts $< 30\%$ or ACA in Ph+ cells (clonal progression), or basophils in blood $\geq 20\%$, or platelets $< 100 \times 10^9 /L$ unrelated to therapy.
- Blastic Phase or Crisis (BP/BC): Blasts in PB or BM $\geq 30\%$, or extramedullary blast cell involvement (with the exception of spleen and liver).
- Death

The date of progression will be defined as the date any of the above criteria is first met. Any subject who has not progressed will be censored on the date of the last examination.

Progression-free survival (PFS) - is defined as the time from dasatinib treatment discontinuation to death (due to any cause) or accelerated phase, or blast crisis. Patients who neither progress nor die will be censored on the date of their last molecular assessment.

Overall survival (OS) - is defined as the time from dasatinib treatment discontinuation to the date of death (due to any cause). Patients who do not die will be censored on their last known alive date.

7.7.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects who maintain MMR (MMR rate) at 12 months after dasatinib discontinuation without re-starting dasatinib treatment in the enrolled subjects in the study. In addition, the MMR rate will also be estimated for the evaluable subjects. Loss of MMR is defined per European Leukemia Net (ELN) definition of progression ([Section 7.6](#)).

7.7.1.1 Primary Analysis

The primary efficacy analysis is to estimate the rate of MMR at 12 months after dasatinib discontinuation without re-starting dasatinib treatment in the enrolled subject population. MMR rate at 12 months and at 6, 24, 36, 48 and 60 months will be summarized by point estimate and Clopper-Pearson two-sided 95% confidence intervals, for the enrolled subject population and the evaluable subject population. Summaries will also be produced for subjects with first line of therapy, and subjects with second/third line of therapy. The summaries for subjects with second/third line of therapy will include two additional columns split between resistance vs intolerance. This will be performed using PROC FREQ with BINOMIAL under options. In the event that any subject discontinues the study or dies prior to analysis timepoint (such as 6, 12... months) then these events will be considered failures and such patients will be included in the denominator of the proportion.

7.7.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include:

- EFS at 12, 24, 36, 48 and 60 months after dasatinib discontinuation;
- RFS at 6, 12, 18, 24 months and every 6 months thereafter after dasatinib discontinuation;
- Assessment of BCR-ABL kinetics for subjects who experience loss of CMR but not MMR;
- Assessment of BCR-ABL kinetics in subjects in CMR with measurable levels;
- The rate of transformation to AP/BC;
- PFS;
- OS.

7.7.2.1 Secondary Analysis

The secondary analysis including EFS rate at 12, 24, 36, 48 and 60 months (including number of subjects with event free at 12, 24, 36, 48 and 60 months, and event free survival rate at 12, 24, 36, 48 and 60 months with 95% CI), RFS rate at 6, 12, 18, 24 months and every 6 months thereafter after dasatinib discontinuation (including number of subjects with relapse free at 6, 12, and 18 month, and relapse free survival rate at 6,12, and 18 months with 95% CI), PFS rate, OS rate, and transformation rate will be estimated using Kaplan-Meier and Brookmeyer-Crowley method. This will be performed using PROC LIFETEST with METHOD=KM and CONFTYPE=LINEAR.

Time from dasatinib discontinuation to loss of MMR (including descriptive statistics for time in days from dasatinib discontinuation to loss of MMR, percentage of patients who were in CMR(MR4.5) at the time of discontinuation and remain in CMR(MR4.5) , percentage of patients who were in CMR(MR4.5) at the time of discontinuation and lost CMR but keep MMR, and percentage of patients keeping CMR(MR4.5) at 12 months after discontinuation), and the rate of transformation to AP/BC/late chronic phase of CML will be summarized using descriptive statistics. These summaries will be produced for the enrolled subject population, the evaluable subject population, subjects with first line of therapy, and subjects with second/third line of therapy. The summaries for subjects with second/third line of therapy will include two additional columns split between resistance vs intolerance.

Kaplan-Meier plots will also be presented for EFS, RFS, PFS, and OS. A forest plot will also be produced for RFS, EFS, PFS, OS, and proportion of subjects who maintain MMR at 12 months.

The estimated 25th percentile, median, and 75th percentile of time to EFS, RFS, PFS and OS and their respective 95% confidence intervals will be provided if applicable.

As specified under [Section 7.6](#) of the statistical analysis plan (SAP), censoring will occur if:

Table 7.7.2.1-1: Time-to-Event Censoring

Time-to-Event Endpoint	Event/Censoring	Event/Censoring Date
EFS	1) Event	Date of Loss of MMR
	2.1) Censoring	Date of Discontinuation (if subjects maintain MMR but discontinue study)
	2.2) Censoring	Last Molecular Measurement Date (if subjects maintain MMR)
	2.3) Censoring	Visit 1 Date (if subjects do not have any post-baseline BCR-ABL assessments)
RFS	1) Event	Date of Relapse (earliest date of loss of MMR, loss of CCyR, loss of CHR, or progression)
	2.1) Censoring	Date of Discontinuation (if subjects maintain MMR, CCyR, CHR, and have no progression but discontinue study)
	2.2) Censoring	Last Molecular Measurement Date (if subjects maintain MMR, CCyR, CHR, have no progression and do not discontinue study)
	2.3) Censoring	Visit 1 Date (if subjects have no post-baseline relapse-related Central Lab Assessments done after Visit 1 Date)

Table 7.7.2.1-1: Time-to-Event Censoring

Time-to-Event Endpoint	Event/Censoring	Event/Censoring Date
PFS	1) Event	Date of Progressive Disease, Date of Death Note: Date of Progressive Disease includes date of events progression to accelerated phase, or blast crisis as defined under Section 7.6 .
	2.1) Censoring	Last Molecular Measurement Date (if subjects have no progression and no death)
	2.2) Censoring	Visit 1 Date (if subjects have no post-baseline progression assessment and no death reported)
OS	1) Event	Date of Death
	2) Censoring	Date of Last Known Alive (if subjects have no death reported)
Transformation to AP/BC	1) Event	Accelerated Phase, or blast crisis phase of CML
	2) Censoring	Last Molecular Measurement Date (if subjects did not develop Accelerated Phase, or blast crisis phase)

Note: Time-to-Event for each Endpoint (EFS, RFS, PFS, OS) will be calculated using the dates in the table above and the following equation: Time-to-EFS/RFS/PFS/OS (months) = [(Date of event/censoring – Date of Last Dasatinib Discontinuation before Study Enrollment) +1] / 30.4375

Assessment of BCR-ABL kinetics for subjects who experience loss of CMR but not MMR, and assessment of BCR-ABL kinetics in subjects in CMR(MR4.5) with measurable levels will be summarized by visit using descriptive statistics. These summaries will be produced for the enrolled subject population, the evaluable subject population, subjects with first line of therapy, and subjects with second/third line of therapy. The summaries for subjects with second/third line of therapy will include two additional columns split between resistance vs intolerance.

A plot (spider or waterfall plot) will also be presented for BCR-ABL level over time for subjects who restarted treatment and it will display percent of BCR-ABL / ABL (IS) versus study months relative to latest dasatinib discontinuation date before study entry.

Time to loss of MMR, re-gaining MMR, re-start of treatment, and time of re-gaining of CMR(MR4.5) will also be displayed on a swimming lane plot using different geometrical figures to distinguish between them.



[REDACTED]

7.8 Safety

The purpose of this section is to describe the safety analyses for the study. All summaries of safety data will be conducted using the enrolled population, following discontinuation of dasatinib and during re-start with dasatinib.

7.8.1 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 will be summarized in the off-treatment, on-treatment screening and on-treatment after restarting dasatinib periods.

AEs of special interest during the off-treatment and on-treatment (during screening and after restarting dasatinib periods) will be summarized by worst NCI CTCAE grade, AEs of special interest categories, and MedDRA system organ class and preferred terms. If a subject experiences multiple AEs under the same preferred term (system organ class), then the subject will be counted only once for that preferred term (system organ class).

Treatment-related AEs, defined as an adverse event which was considered to be related will be summarized during the on-treatment after restarting dasatinib period. If a subject experiences multiple occurrences of the same AE with different relationship to study medication categories,

the subject will be counted once, as a relationship category of treatment-related. In the event the relationship to study drug is 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 according to NCI CTCAE, Version 4.0. If a subject 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.”

Tables summarizing the number of patients experiencing AEs and patient incidence for AEs will be generated for each of the following:

- Overall summary of AEs
- All AEs by worst CTCAE grade category
- Treatment-related AEs by worst CTCAE grade category
- Serious AEs
- Treatment-related serious AEs
- AEs with action taken as study drug withdrawn
- AEs leading to study discontinuation
- AEs with fatal outcome.

The worst NCI CTCAE for treatment-related AEs will also be summarized for the number of dose interruptions, dose reductions and treatment discontinuations. Adverse events due to intolerance of study treatment will also be summarized.

Corresponding by-patient data listings for adverse events will be provided in on-treatment screening, off-treatment, and on-treatment after restarting dasatinib periods.

7.8.2 Adverse Events of Special Interest

The following AEs of special interest will consist of any:

- Musculoskeletal disorders
- Connective tissue disorders
- Vascular disorders

The following summaries will be provided for AEs of special interest:

- AEs of special interest by preferred terms
- AEs of special interest by worst CTCAE grade
- AEs of special interest with action taken as study drug withdrawn
- AEs of special interest with action taken as study treatment reduced, interrupted, or discontinued.

In addition, withdrawal syndrome after dasatinib discontinuation will be summarized. Subjects who need treatment after withdrawal syndrome will be listed.

7.8.3 *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 during off-treatment and on-treatment study periods. Echocardiogram and chest x-ray measurements will be documented at baseline and during off-treatment and on-treatment study periods only if clinically indicated.

Electrocardiograms (ECGs), echocardiogram, and chest x-ray measurements will be summarized by visit during off-treatment and on-treatment periods.

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

7.8.4 *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.

7.8.4.1 *Hematology*

The worst NCI CTCAE grade for white blood cell (WBC) counts, absolute neutrophil counts (ANC), basophils (% and absolute), platelet counts, and hemoglobin will be summarized during off-treatment (upon discontinuation of dasatinib) and on-treatment study periods.

A summary of hematology lab results and changes from baseline by visit during off-treatment and on-treatment study periods may also be needed.

7.8.4.2 *Serum Chemistry*

The worst NCI CTCAE grade for AST (SGOT), ALT (SGPT), total bilirubin, and serum creatinine will be summarized during off-treatment (upon discontinuation of dasatinib) and on-treatment study periods.

A summary of serum chemistry lab results and changes from baseline by visit during off-treatment and on-treatment study periods may also be needed.

7.8.5 *Vital Signs*

Vital sign measurements (systolic blood pressure (BP), diastolic BP, heart rate, respiratory rate, and temperature) will be summarized by visit during the off-treatment and on-treatment study periods.

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

7.8.6 *Physical Examination*

Physical examination parameters will be summarized by visit during the off-treatment and on-treatment study periods.

7.8.7 *Pregnancy*

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

[REDACTED]

8 INTERIM ANALYSIS

8.1 General Information

An IDMC will be convened with experts not otherwise involved with the study team. During the course of the study, the IDMC will conduct regular reviews (at least 2 times per year and ad-hoc as necessary) of safety data and efficacy data listings and pharmacovigilance reports. Operational details for the IDMC, as well as the timing of analyses, monitoring guidelines, and content of the reports will be detailed in the IDMC charter.

8.1.1 Statistical Approaches

There will be an interim analysis when 30 patients have been followed until month 12 (calculated from discontinuation of dasatinib). This analysis will focus on specific efficacy endpoints such as MMR, time from discontinuation to loss of MMR, deep molecular response, EFS and other endpoints for the enrolled population. In addition, standard safety data will be presented.

The interim analysis will be performed using the data collected by the cutoff date for the interim analysis. All patients enrolled prior to the cutoff date will be included in the interim analysis and all data up to the cutoff date will be summarized or listed.

9 CONVENTIONS

Unless specified otherwise, the following conventions will be used for imputing partial 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 month are missing, “July 1” will be used to replace the missing day and month.
- If a date is completely missing, no imputation is needed. The date will be considered missing.

For dasatinib start date:

- If only the day of the month is missing, the last day of the month will be used to replace the missing day.
- If the day and month are missing or the date is completely missing, no imputation is needed. The date will be considered missing.

For adverse events:

- If only the day 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.

10 CONTENT OF REPORTS

The complete list of analyses contributing to the clinical study report is given in the Data Presentation Plan.

APPENDIX 3 STUDY ASSESSMENTS AND PROCEDURES

Table 11-2: Screening and Baseline Assessments

Procedure	Screening 1	Screening 2	Visit 1 (Baseline)	Notes
<ul style="list-style-type: none"> • Visit 1 window is open until all entry criteria are satisfied unless otherwise specified. • Screening 2: 90 days ± 10 days after Screening 1. 				
Eligibility Assessments				
Informed Consent	X			
Inclusion/Exclusion Criteria	X	X		Serum chemistry and CBC with diff, platelets: Visit 1 only, within 72 hrs prior to study entry
Serology for Hepatitis B virus		X		Hepatitis B surface antigen (HBsAg) and antibody to Hepatitis B core antigen (also known as total hepatitis B core antibody; anti-HBc). Hepatitis B serologic testing to be conducted at any time during screening or at Visit 1. HBV testing results within 1 year prior to Visit 1 are permitted. Results must be recorded on the CRF. See Study Protocol Section 5.3 for recommendations regarding subjects with positive HBV serology.
Medical History	X		X	
Pregnancy Test	X		X	At screening
Review Contraception Requirements	X		X	Review contraception requirements presented in Study Protocol Section 3.3.1 and Appendix 8 with both WOCBP and male subjects.
Safety Assessments				
Physical Examination, vital signs and Performance Status (PS)/Sokal (or Hasford) score			X	
Assessment of signs and symptoms			X	
Concomitant medications			X	
Adverse event assessment			X	

Table 11-2: Screening and Baseline Assessments

Procedure	Screening 1	Screening 2	Visit 1 (Baseline)	Notes
				<ul style="list-style-type: none"> • Visit 1 window is open until all entry criteria are satisfied unless otherwise specified. • Screening 2: 90 days ± 10 days after Screening 1.
ECG			X	
Echocardiogram			X	Only if clinically indicated
Serum chemistry			X	Within 72 hrs prior to study entry.
Chest X-ray			X	Chest X-ray only if clinically indicated, or there is evidence of shortness of breath.
Efficacy-related Laboratory tests				
CBC with diff, platelets			X	Within 72 hrs prior to study entry.
Mutational analysis			X	Blood sample to be stored and analyzed later if mutations are detected in other assessments during the study
Molecular analysis (Q-PCR)	X	X		Q-PCR labs will be performed in a centralized lab and expressed on an international scale (IS) Screening 2 molecular analysis (90 days after Screening 1 assessment) is required to confirm CMR (MR4.5).
Patient-reported Outcomes (MDASI)-CML symptom-burden assessment			X	Patient must complete the PROs during the study visit: at the beginning of the visit is preferred.
EORTC-QLC-C30 assessment			X	PRO assessments are not required and are not applicable to patients who had a legally accepted representative sign the informed request at study entry.

Table 11-2: Screening and Baseline Assessments

Procedure	Screening 1	Screening 2	Visit 1 (Baseline)	Notes
Health Care Resource Utilization Assessment			X	<ul style="list-style-type: none"> • Visit 1 window is open until all entry criteria are satisfied unless otherwise specified. • Screening 2: 90 days ± 10 days after Screening 1.
Clinical Drug Supplies				<p>Dasatinib will be discontinued after all screening criteria are met and baseline assessments are completed.</p>

Table 11-3: On Study Assessment: Off Treatment (Dasatinib Discontinued) Assessments

Procedure	Off Treatment ^{a,b}	Notes
Safety Assessments		
Physical Examination, vital signs and Performance Status (PS)	Every 3 months	<ul style="list-style-type: none"> • Visit window is ± 10 days for assessment every 3 or 6 months. ± 5 days for monthly assessments. • Assessments will continue throughout the 5 year study period.
Assessment of signs and symptoms	Every 3 Months	
Adverse event assessment	Every 3 Months	<p>If a pt is taken off study due to AE, follow-up visits are required q 4 weeks until toxicities resolve to baseline or Grade ≤ 1, stabilize, or are deemed irreversible.</p>
Concomitant medications	Every 3 Months	
ECG	As clinically indicated	
Echocardiogram	As clinically indicated	
Serum chemistry	Every 3 months	
HBV Serology	Only once for subjects not previously tested within 1 year prior to Visit 1.	<p>HBV serology test results must be recorded in the CRF.</p> <p>See Section 5.3 for recommendations for subjects with positive HBV serology.</p>
Chest X-ray	As clinically indicated	
Pregnancy test	X	<p>One month after discontinuation of dasatinib.</p>
Review Contraception Requirements	X	<p>Review contraception requirements presented in Section 3.3.1 and Appendix 8 with both WOCBP and male subjects</p>

Table 11-3: On Study Assessment: Off Treatment (Dasatinib Discontinued) Assessments

Procedure	Off Treatment ^{a,b}	Notes
Efficacy Assessments		
CBC with diff, platelets	Every 3 months	CBC may be done more frequently if clinically indicated.
Cytogenetics	At loss of MMR. ^b	Bone marrow aspirate/biopsy or peripheral blood (FISH) will be performed within 4 weeks of loss of MMR. For adequate cytogenetic results, peripheral blood (FISH) should ideally be performed when the ANC > 500/mm ³
Molecular analysis/Q-PCR	Year 1: Monthly Year 2-5: Every 3 months (see note for exceptions)	Q-PCR analyses to be performed in a centralized lab and expressed in International Scale units Exceptions to Years 2-5, 3 monthly assessment <ul style="list-style-type: none"> Subjects with BCR-ABL kinetics who experience the first episode of intermittent loss of CMR (MR4.5) (“blips” but no MMR loss), will have Q-PCR levels measured monthly for 3 months after the event. If MMR is maintained, Q-PCR levels will continue to be measured every 3 months.
Mutational analysis	X	Mutational Analysis will be conducted any time there is loss of MMR, loss of CCyR or Loss of CHR. Samples to be drawn and stored for future exploratory analysis.

Table 11-3: On Study Assessment: Off Treatment (Dasatinib Discontinued) Assessments

Procedure	Off Treatment ^{a,b}	Notes
Patient-reported outcomes		
(MDASI) CML symptom burden assessment	Every 6 months and at loss of MMR ^b	<ul style="list-style-type: none"> • Visit window is ± 10 days for assessment every 3 or 6 months. ± 5 days for monthly assessments. • Assessments will continue throughout the 5 year study period. <p>Patient must complete the PROs during the study visit: at the beginning of the visit is preferred.</p>
EORTC-QLC-C30	Every 6 months and at loss of MMR ^b	<p>PRO assessments are not required and are not applicable to patients who had a legally accepted representative sign the informed request at study entry.</p>
Health Care Resource Utilization Assessment	Every 3 months	<p>Health care resource utilization will be assessed at each visit.</p>

MMR = major molecular response; CCyR = complete cytogenetic response; CMR= complete molecular response (MR4.5); Month = 30 days

^a During the off-treatment period, each assessment time point is counted from Visit 1, the day dasatinib was discontinued.

^b Patients with loss of MMR during the off-treatment period will be restarted on dasatinib at the dose received before dasatinib was discontinued at study entry. See Study protocol Table 5.1-3 for study assessments at dasatinib restart and during treatment with dasatinib.