

Page: 1  
Protocol Number: CA180406  
IND Number: 66,971  
Ex-US Non-IND  
EUDRACT Number 2012-001421-27  
Date: 08-Apr-2013  
Revised Date 24-Jul-2017

## **Clinical Protocol CA180406**

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

**Revised Protocol Number: 04**

### **Study Director/Medical Monitor**

Patricia Martín-Regueira MD

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**This document is the confidential and proprietary information of Bristol-Myers Squibb Company and its global affiliates (BMS). By reviewing this document, you agree to keep it confidential and to use and disclose it solely for the purpose of assessing whether your organization will participate in and/or the performance of the proposed BMS-sponsored study. Any permitted disclosures will be made only on a confidential "need to know" basis**

**within your organization or to your independent ethics committee(s). Any other use, copying, disclosure or dissemination of this information is strictly prohibited unless expressly authorized in writing by BMS. Any supplemental information (eg, amendments) that may be added to this document is also confidential and proprietary to BMS and must be kept in confidence in the same manner as the contents of this document. Any person who receives this document without due authorization from BMS is requested to return it to BMS or promptly destroy it. All other rights reserved. References to BMS in this protocol may apply to partners to which BMS has transferred obligations, e.g., a Contract Research Organization (CRO).**

Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.















## SYNOPSIS

### Clinical Protocol CA180406

**Protocol Title:** 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

**Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):** At study entry, dasatinib will be discontinued in all enrolled patients. Dasatinib will be restarted if major molecular response is lost during the off-treatment period at the dose level received before study entry. The patient will remain on treatment for the duration of the study. Dose adjustment for toxicity and response is permitted during the retreatment period based on protocol guidelines. Dosing above 180 mg QD of dasatinib is prohibited.

**Study Phase:** Phase 2

**Research Hypothesis:** CP-CML patients with stable complete molecular response (CMR) who discontinue dasatinib treatment are able to maintain a sustained remission in the long-term, with undetectable or minimally detectable BCR-ABL residual disease.

**Objectives:** The primary objective of this study is to assess the rate of major molecular response (MMR), defined as the proportion of subjects who maintain MMR (BCR-ABL transcripts < 0.1% on International Scale (IS)) at 12 months after dasatinib discontinuation, without re-starting dasatinib treatment.

The secondary objectives of this study include assessment of the following: event-free survival (EFS) (defined as no loss of MMR) at 12, 24, 36, 48 and 60 months after dasatinib discontinuation; relapse-free survival (RFS) at 6, 12, 18, 24 months and every 6 months thereafter; BCR-ABL kinetics in those patients who experience intermittent loss of CMR (MR<sup>4.5</sup>) but no loss of MMR (ie, BCR-ABL blips); assessment of BCR-ABL kinetics in patients who are in CMR (MR<sup>4.5</sup>) or less when transcript levels are still measurable; rate of transformation to accelerated phase/blast crisis (AP/BC); progression free survival, and overall survival.

**Study Design:** This is an open-label, single-arm study in adult patients with CP-CML who have received dasatinib as treatment for a minimum of 2 years at the time of enrollment and have confirmed dasatinib-induced complete molecular remission (defined as  $\geq 4.5$ -log reduction of BCR-ABL transcript as determined by local standards) ongoing for at least 1 year prior to study entry. Eligible patients must have achieved a 1-log reduction in BCR-ABL transcript levels compared to baseline as determined by local standards or less than or equal to 10% IS [International Standard]) at 3 months for current dasatinib therapy.

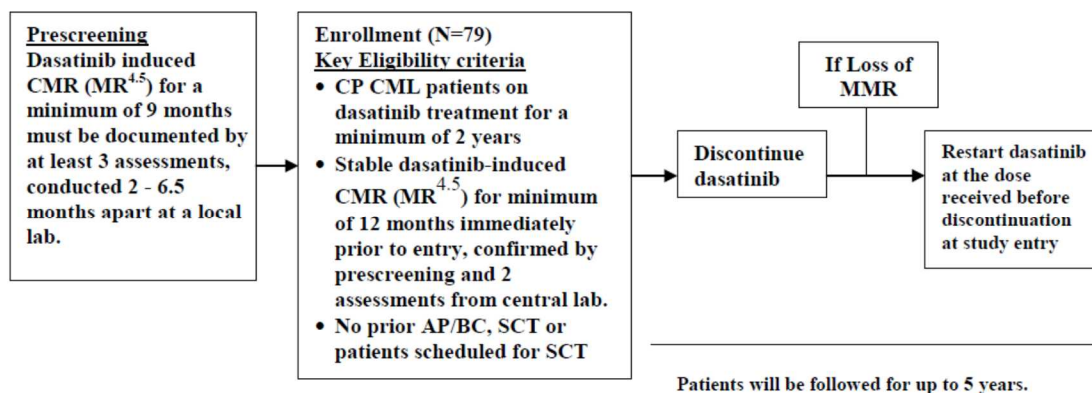
Prospective patients will have been prescreened to confirm dasatinib-induced CMR stable for a minimum of 9 months at a local laboratory prior to the first study sponsored screening assessment. CMR must be documented by at least 3 assessments, 2 - 6.5 months apart conducted at a local lab. Once stable 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 3 months. Patients are eligible for enrollment if both assessments from the central lab confirm CMR (MR<sup>4.5</sup>). For any patient not eligible for enrollment on the basis of a central laboratory test that does not confirm CMR, rescreening is allowed 9 months (or longer) after the time of the last central lab screening failure.

Once all entry criteria are met, patients will be enrolled. At the time of enrollment, dasatinib will be discontinued.

Patients will be monitored for maintenance of MMR (BCR-ABL transcripts < 0.1% IS). At the loss of MMR, dasatinib treatment will be resumed at the dose level the patient received before dasatinib was discontinued at study entry. Patients who have restarted treatment with dasatinib 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](#).

A rise of PCR > 0.0032% (4.5 log reduction) 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.



**AP/BC =accelerated phase/blast crisis; CMR = complete molecular response.**

**IS = International Scale; SCT = stem cell transplant; Month = 30 days**

**CMR (MR4.5) defined as ≤ 0.0032% (IS) or ≥ 4.5 log reduction of BCR-ABL transcript as determined by local standards**

**Study Population:** CP CML patients on dasatinib treatment for a minimum of 2 years with confirmed stable dasatinib-induced CMR (MR<sup>4.5</sup>) for a minimum of 12 months prior to enrollment and no prior accelerated phase/blast crisis (AP/BC) or stem cell transplant (SCT). Eligible patients must have achieved a 1-log reduction in BCR-ABL transcript levels compared to baseline as determined by local standards, or less than or equal to 10% IS [International Standard]) at 3 months for current dasatinib therapy. Patients eligible for SCT are not eligible for this study. Eligible patients must meet all prescreening and screening criteria.

**Study Assessments:** Safety assessments include: physical examination (including vital signs and performance status), signs and symptoms, serum chemistry, ECG (baseline and if clinically indicated), echocardiogram, and chest x-ray as (both as if clinically indicated). Adverse events will be assessed throughout this study using the current version of the NCI CTCAE guide. Efficacy assessments include: complete blood count (CBC) with differential, platelets, cytogenetics (if clinically indicated), and molecular analysis (qualitative polymerase chain reaction [Q-PCR]). Patient-reported outcomes will be assessed by the MDASI-CML QOL questionnaire (severity and impact of cancer-related symptoms) and the EORTC-QLQ-C30 questionnaire (self-reported measure of quality of life). The schedule of study assessments is presented in [Section 5.1](#), Flow Chart/Time and Events Schedule.

#### Statistical Considerations:

**Sample Size:** This is an open label single arm study with no comparative objective. Under the assumption of a 75% MMR rate at 12 months after dasatinib discontinuation, 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.

**Endpoints:** The primary endpoint is the MMR rate at 12 months after dasatinib discontinuation. Secondary endpoints include event-free survival (EFS) at 12 months, relapse-free survival (RFS) at 6, 12, 18, 24 months and every 6 months thereafter after dasatinib discontinuation, assessment of BCR-ABL kinetics, the rate of transformation to AP/BC, progression free survival (PFS) and overall survival (OS). Exploratory endpoints include identifying prognostic factors for maintaining MMR at 12 months after dasatinib discontinuation without re-starting dasatinib, e.g. age (years), gender (male/female), Sokal risk group, time from diagnosis (months), time in dasatinib-induced stable CMR (MR4.5) prior to discontinuation (months), occurrence of BCR-ABL blips (changes in residual level that do not have clinical relevance and does not imply loss of MMR) (Yes/No), history of pleural effusion (Yes/No), history of lymphocytosis (Yes/No) (lymphocytes  $> 3.6 \times 10^9/L$ ); the proportion of subjects who achieve molecular response and cytogenetic response after relapse; time to molecular re-response (rMMR and rCMR) and cytogenetic re-response (rCCyR and rPCyR) after re-initiating dasatinib in patients who lose MMR after discontinuation; healthcare resource utilization that is incurred during discontinuation of study treatment and during treatment (re-start of dasatinib); the frequency and CTCAE grade of adverse events during discontinuation of study treatment and during treatment (re-start of dasatinib); and quality of life assessments: EORTC-QLQ-C30 and MDASI-CML (following discontinuation of study treatment and during treatment).

**Analyses:** No formal statistical testing will be performed. Summary statistics will be provided for subject disposition, baseline characteristics (demographics, medical history, etc.), dosing, efficacy, safety, and health outcome endpoints using the enrolled subject population. Also, efficacy will be summarized using the evaluable subject population. Health resource utilization data will be assessed using descriptive statistics and will be reported in an analysis separate from the clinical study report.

Efficacy will be described for each of the following subgroups: patients in CMR ( $MR^{4.5} \leq 24$  months or  $> 24$  months prior to dasatinib discontinuation, patients' with dasatinib as first line or second/third line treatment.

MMR rate at 12 months will be summarized by point estimate and Clopper-Pearson two-sided 95% confidence intervals. EFS at 12, 24, 36, 48 and 60 months, RFS at 6, 12, 18, 24 months and every 6 months thereafter, the proportion of subjects who achieve molecular response after relapse, rate of transformation to AP/BC, and rate of OS will be estimated using Kaplan-Meier method.

Time to event endpoints including EFS, RFS, time to re-gaining MMR and CMR for subjects who experience MMR loss and re-start dasatinib, PFS, and OS will be summarized using Kaplan-Meier estimates and Brookmeyer-Crowley methods. Censoring details are provided in the protocol and will be further specified in the statistical analysis plan (SAP).

Exploratory analysis to identify prognostic factors will be analyzed using Cox Proportional Hazard models.

**Interim Analysis:** The Sponsor will conduct continuous review and reporting of safety throughout the study as required by GCP and routine pharmacovigilance standards.

In case of any progression from chronic phase through accelerated or blast crisis during the discontinuation phase, the steering committee and the internal data monitoring committee (IDMC) will be consulted and the case will be discussed to decide potential early study termination.

An interim analysis is planned when all patients have been followed until month 12 (calculated from discontinuation of dasatinib). This analysis will assess specific safety and efficacy endpoints and will be detailed in the statistical analysis plan.

Regular reviews (at least 2 times a year and ad-hoc as necessary) 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.

## TABLE OF CONTENTS

TITLE PAGE .....	1
DOCUMENT HISTORY .....	3
[REDACTED] .....	6
[REDACTED] .....	6
SYNOPSIS .....	9
TABLE OF CONTENTS .....	12
1. INTRODUCTION AND STUDY RATIONALE .....	15
[REDACTED] .....	16
1.2 Research Hypothesis .....	17
1.3 Objectives(s) .....	17
1.3.1 Primary Objectives .....	17
1.3.2 Secondary Objectives .....	17
[REDACTED] .....	18
[REDACTED] .....	18
1.5 Overall Risk/Benefit Assessment .....	19
2. ETHICAL CONSIDERATIONS .....	20
2.1 Good Clinical Practice .....	20
2.2 Institutional Review Board/Independent Ethics Committee .....	20
2.3 Informed Consent .....	20
3. INVESTIGATIONAL PLAN .....	21
3.1 Study Design and Duration .....	21
3.2 Post Study Access to Therapy .....	23
3.3 Study Population .....	23
3.3.1 Inclusion Criteria .....	23
3.3.2 Exclusion Criteria .....	24
3.3.3 Women of Childbearing Potential .....	26
3.4 Concomitant Treatments .....	27
3.4.1 Prohibited and/or Restricted Treatments .....	27
3.4.2 Other Restrictions and Precautions .....	27
3.5 Discontinuation of Subjects from Treatment or from Study .....	28
3.6 Post Treatment Study Follow up .....	29
3.6.1 Withdrawal of Consent .....	29
3.6.2 Lost to Follow-Up .....	29
4. TREATMENTS .....	29
4.1 Study Treatments .....	30
4.1.1 Investigational Product .....	31
4.1.2 Non-investigational Product .....	31
4.1.3 Handling and Dispensing .....	31
4.2 Method of Assigning Subject Identification .....	31
4.3 Selection and Timing of Dose for Each Subject .....	31
4.3.1 Dose Adjustments .....	32
4.3.1.1 Dose Escalation .....	32
4.3.1.2 Dose Reduction Guidelines .....	32
4.4 Blinding/Unblinding .....	34

4.5 Treatment Compliance.....	35
4.6 Destruction and Return of Study Drug .....	35
4.6.1 Destruction of Study Drug .....	35
4.6.2 Return of Study Drug .....	35
4.7 Retained Samples for Bioavailability / Bioequivalence .....	36
5. STUDY ASSESSMENTS AND PROCEDURES.....	37
5.1 Flow Chart/Time and Events Schedule.....	37
5.2 Study Materials .....	47
5.3 Safety Assessments.....	47
5.3.1 Safety endpoints .....	48
5.4 Efficacy Assessments.....	48
5.4.1 Efficacy Endpoints .....	48
5.4.1.1 Definition of Hematologic Response .....	48
5.4.1.2 Definition of Cytogenetic Response.....	49
5.4.1.3 Definition of Molecular Response .....	49
5.4.1.4 Event free survival .....	49
5.4.1.5 Relapse (during off treatment period).....	49
5.4.1.6 Progression free survival.....	50
5.4.2 Progression.....	50
5.4.3 Overall Survival.....	50
5.5 Pharmacokinetic Assessments .....	50
5.6 [REDACTED] .....	50
5.7 Outcomes Research Assessments .....	50
5.8 [REDACTED] .....	50
5.8 [REDACTED] .....	51
5.8 Other Assessments .....	51
5.8.1 Hematology.....	51
5.8.2 Serum chemistry Tests.....	52
5.8.3 Bone Marrow/Peripheral Blood (FISH).....	52
5.8.4 Molecular Analysis .....	52
5.8.5 Pregnancy Test.....	52
5.9 Results of Central Assessments .....	52
6. ADVERSE EVENTS.....	53
6.1 Serious Adverse Events .....	53
6.1.1 Serious Adverse Event Collection and Reporting.....	54
6.2 Nonserious Adverse Events .....	55
6.2.1 Nonserious Adverse Event Collection and Reporting.....	55
6.3 Laboratory Test Result Abnormalities.....	55
6.4 Pregnancy.....	55
6.5 Overdose .....	56
6.6 Potential Drug Induced Liver Injury (DILI) .....	56
6.7 Other Safety Considerations .....	56
7. DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES.....	57
8. STATISTICAL CONSIDERATIONS.....	57
8.1 Sample Size Determination.....	57

8.2 Populations for Analyses .....	57
8.3 Endpoints .....	57
8.3.1 Primary Endpoint(s) .....	57
8.3.2 Secondary Endpoint(s).....	58
[REDACTED] .....	58
8.3.4 Safety Endpoints.....	58
[REDACTED] .....	58
8.4 Analyses.....	58
8.4.1 Demographics and Baseline Characteristics.....	59
8.4.2 Efficacy Analyses .....	59
8.4.3 Safety Analyses.....	59
8.4.4 Pharmacokinetic Analyses .....	59
[REDACTED] .....	60
[REDACTED] .....	60
8.4.7 Other Analyses .....	60
8.5 Interim Analyses .....	60
9. STUDY MANAGEMENT .....	60
9.1 Compliance .....	60
9.1.1 Compliance with the Protocol and Protocol Revisions .....	60
9.1.2 Monitoring .....	61
9.1.3 Investigational Site Training.....	61
9.2 Records .....	61
9.2.1 Records Retention .....	61
9.2.2 Study Drug Records .....	62
9.2.3 Case Report Forms .....	62
9.3 Clinical Study Report and Publications .....	63
10. GLOSSARY OF TERMS .....	64
11. LIST OF ABBREVIATIONS.....	65
[REDACTED] .....	68
APPENDIX 1 PREGNANCY TESTING LOG .....	71
[REDACTED] .....	74
APPENDIX 3 MEDICAL CONDITIONS AND DRUGS WHICH MAY CAUSE QTC PROLONGATION AND TORSADE DE POINTES (NOT ALL INCLUSIVE) .....	75
APPENDIX 4 COMMON CYP3A4 SUBSTRATES (NOT ALL INCLUSIVE).....	76
APPENDIX 5 COMMON CYP3A4 INHIBITORS (NOT ALL INCLUSIVE) .....	78
APPENDIX 6 COMMON CYP3A4 INDUCERS (NOT ALL INCLUSIVE).....	79
APPENDIX 7 SOKAL AND HASFORD: CALCULATION OF RELATIVE RISK.....	80
APPENDIX 8 METHODS OF CONTRACEPTION .....	81







## 1.2 Research Hypothesis

CP-CML patients treated with dasatinib for a minimum of 2 years who have achieved stable CMR (defined as dasatinib-induced MR4.5 for a minimum of 12 months before study entry), who discontinue dasatinib treatment are able to maintain a sustained remission in the long-term, with undetectable or minimally detectable BCR-ABL residual disease.

In this trial, CMR is defined as  $\leq 0.0032\%$  or  $\geq 4.5$  log reduction of BCR-ABL transcript levels.

## 1.3 Objectives(s)

### 1.3.1 Primary Objectives

The primary objective of this study is to assess the rate of MMR, defined as the proportion of subjects who maintain MMR (BCR-ABL transcripts  $< 0.1\%$  on International Scale<sup>13,14</sup>) at 12 months after dasatinib discontinuation, without re-starting dasatinib.

### 1.3.2 Secondary Objectives

The secondary objectives of this study are to assess the following:

- Event-free survival (defined as survival with no loss of MMR) [[Section 5.4.1.3](#)] at 12, 24, 36, 48 and 60 months after dasatinib discontinuation
- Relapse-free survival at 6, 12, 18, 24 months and every 6 months thereafter. Relapse is defined in [Section 5.4.1.4](#)
- Assessment of BCR-ABL kinetics in those patients who experience loss of CMR (MR<sup>4.5</sup>) but no loss of MMR (BCR-ABL kinetics are any changes in residual level that do not have clinical relevance)
- Assessment of BCR-ABL kinetics in patients who are in CMR (MR<sup>4.5</sup>) or less where transcript levels are still measurable
- Rate of transformation to AP/BC
- Progression free survival
- Overall survival.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## 1.5 Overall Risk/Benefit Assessment

Dasatinib has demonstrated a favorable risk-benefit profile in patients resistant or intolerant to imatinib and in newly diagnosed patients with CP-CML.

Although maintenance therapy with imatinib or a second-generation TKIs such as dasatinib, are generally well tolerated for most patients, chronic toxicities (even if low grade) can impair a patient's daily quality of life.<sup>8</sup> In addition, there is potential for late-emerging toxicities that could develop, given that the current experience with TKIs only spans little more than a decade.<sup>8</sup>

Dasatinib is potentially harmful to the developing fetus, and pregnancy must be avoided during treatment periods. In this study, investigators will counsel women of childbearing potential and male subjects who are sexually active with women of child bearing potential on the importance of pregnancy prevention and the implications of an unexpected pregnancy during treatment with dasatinib.

For these reasons, one critical goal of CML treatment is to identify those patients who may be able to achieve long-lasting disease remission, without the need for ongoing treatment.

This trial will generate data by following patients for 5 years after treatment discontinuation, and assessing long-term stability of CMR (MR<sup>4.5</sup>) achieved on dasatinib, recurrence rate, patients quality of life off dasatinib treatment and, importantly, the ability to regain a molecular response in those patients who relapse after treatment withdrawal.

Patients who have attained a sustained CMR (MR<sup>4.5</sup>) while receiving dasatinib 100 mg QD,<sup>2</sup> given either as first or as second line treatment, will be eligible for this study.

The rationale for this trial supports the hypothesis that the benefit of maintaining the deepest level of response achieved with dasatinib predicts better long-term disease control and outcome and might theoretically cure some patients who are newly diagnosed with CP CML. Moreover, the risk of being off treatment is balanced by the expectation of an increased quality of life: in fact, drug-related side effects,<sup>19</sup> even if manageable, impose an additional burden of morbidity and may be associated with reduced treatment compliance.<sup>8,20</sup>

## **2. ETHICAL CONSIDERATIONS**

### **2.1 Good Clinical Practice**

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

### **2.2 Institutional Review Board/Independent Ethics Committee**

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator or BMS should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

### **2.3 Informed Consent**

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

- 1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- 2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
- 3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
- 4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
- 5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
- 6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

Subjects unable to give their written consent (eg, stroke or subjects with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this subject become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

### **3. INVESTIGATIONAL PLAN**

#### **3.1 Study Design and Duration**

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  $\geq 4.5$ -log reduction of BCR-ABL transcript as determined by local standards) ongoing for at least 1 year immediately prior to study entry.

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 (MR<sup>4.5</sup>).

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

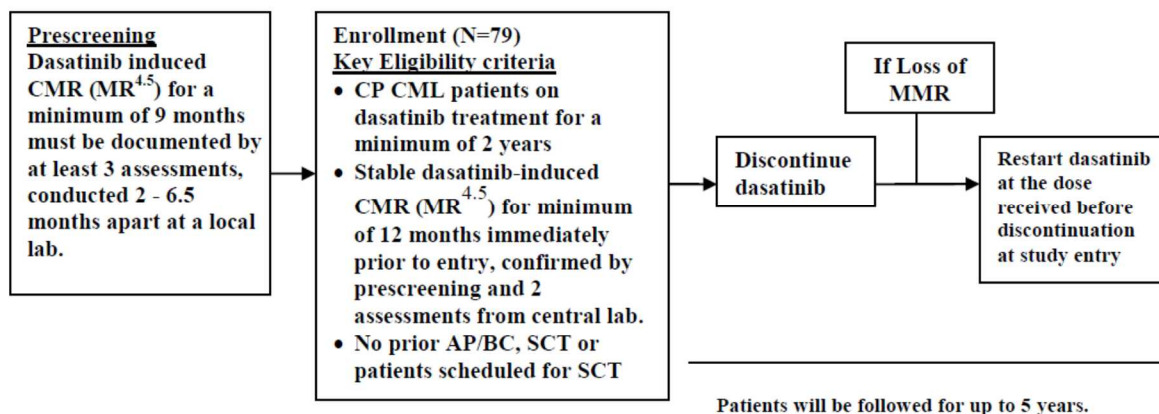
Patients will be monitored for maintenance of MMR (BCR-ABL transcripts  $< 0.1\%$  IS). In case of loss of MMR, dasatinib treatment will be resumed at the dose level the patient was receiving before dasatinib was discontinued at study entry. Patients who have restarted treatment due to loss of MMR will 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.

A rise of PCR  $> 0.0032\%$  (4.5 log reduction) 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 3.1-1.

**Figure 3.1-1: 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<sup>4.5</sup>) defined as  $\leq 0.0032\%$  (IS) or  $\geq 4.5$  log reduction of BCR-ABL transcript as determined by local standards

### **3.2 Post Study Access to Therapy**

At the end of the study, BMS will not continue to supply study drug to subjects/investigators unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

### **3.3 Study Population**

For entry into the study, the following criteria **MUST** be met.

#### **3.3.1 Inclusion Criteria**

##### **1. Signed Written Informed Consent**

- a) Patients must be informed of the investigational nature of this study and of alternative standard therapeutic options and must provide written informed consent.

##### **2. Target Population**

- a) Men and women diagnosed with CP-CML, on treatment with dasatinib for a minimum of 2 years at the time of enrollment and in dasatinib-induced complete molecular remission (defined as  $\leq 0.0032\%$  or  $\geq 4.5$  log reduction of BCR-ABL transcript as determined by local standards) ongoing for at least 1 year prior to study entry.
  - i) Patients are eligible for the screening assessment from the central lab if they have been in stable dasatinib induced CMR for a minimum of nine months, documented by at least three assessments, conducted 2 - 6.5 months apart, at a local lab. The first screening assessment conducted at the central lab will be repeated after three months, if the first assessment confirms CMR (MR<sup>4.5</sup>). Patients are eligible for enrollment if both assessments from the central lab confirm MR<sup>4.5</sup>. For any patient not eligible for enrollment on the basis of a central laboratory test that does not confirm CMR, rescreening is allowed 9 months after (or longer) from the last central lab screening failure. These patients must have documented stable CMR at the local lab, and must meet all other criteria, before rescreening.
- b) Subjects who have received dasatinib beyond first or second line treatment and meet other enrollment criteria are eligible for the study provided prior TKIs were discontinued due to intolerance or lack efficacy, although only one instance of lack of efficacy to TKI is allowed.
- c) ECOG PS of 0-1 ([Appendix 2](#))
- d) Life expectancy of > 1 year
- e) Adequate renal function defined as serum creatinine  $\leq 3.0$  times the institutional ULN
- f) Adequate hepatic function defined as: total bilirubin  $\leq 3.0$  times the institutional ULN; alanine aminotransferase (ALT) and aspartate aminotransferase (AST)  $\leq 5$  times the institutional upper limit of normal (ULN).

In cases where the patient needs to restart dasatinib therapy, caution will be used in case of hepatic impairment.

- g) Serum Na, K, Mg, and total serum Ca or ionized Ca levels must be greater than or equal to the institutional lower limit of normal. Patients with low K, Mg levels, total serum Ca and/or ionized Ca may be repleted to allow for protocol entry. Rescreening is permitted in the event of temporary biochemical abnormalities.
- h) Not applicable per Amendment 02.

### 3. Age and Reproductive Status

- a) Men and women, ages  $\geq 18$
- b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the restart of study drug.
- c) Women must not be breastfeeding
- d) WOCBP must agree to follow instructions for method(s) of contraception at the restart of treatment with study drug (dasatinib) and for the duration treatment plus 30 days (duration of ovulatory cycle) for a total of 30 days post-treatment completion.
- e) Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for 90 days after study entry (withdrawal of dasatinib), at restart of study drug (dasatinib) and for the duration of treatment with study drug (dasatinib) plus 90 days (duration of sperm turnover) for a total of 90 days post-treatment completion.
- f) Male subjects whose partners are WOCBP must use condoms, including male subjects who are azoospermic. WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements but still must undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of  $< 1\%$  per year when used consistently and correctly

At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed in [Appendix 8](#).

#### 3.3.2 Exclusion Criteria

##### 1. Target Disease Exceptions

- a) Not applicable per Amendment 02.
- b) Patients who have not achieved a 1-log reduction in BCR-ABL transcript levels compared with baseline as determined by local standards or  $> 10\%$  IS [International Standard]) documented at 3.0-6.5 months since the initial start of dasatinib therapy.



- c) Patients who have previously undergone hematopoietic stem cell transplantation (SCT) or who are scheduled for SCT
- d) Not applicable per Amendment 02.
- e) Previous diagnosis of CML accelerated phase or blast crisis.

## **2. Medical History and Concurrent Diseases**

- a) Prior or concurrent malignancy, except the following:
  - i) Curatively treated basal cell or squamous cell skin cancer
  - ii) Cervical carcinoma in situ
  - iii) Adequately treated Stage I or II cancer from which the subject is currently in complete remission
  - iv) Any other cancer from which the subject has been disease free for 3 years
- b) A serious uncontrolled medical disorder or active infection that would impair the ability of the subject to receive protocol therapy in case re-initiation of dasatinib is needed.
  - i) Although subjects with acute hepatitis B virus (HBV) infection are excluded, subjects with chronic or resolved hepatitis B infection may be enrolled if they meet all other eligibility criteria. See [Section 5.3](#) for recommendations regarding subjects with positive HBV serology.
- c) Uncontrolled or significant cardiovascular disease, including any of the following:
  - i) Not Applicable per Amendment 02.
  - ii) Diagnosed or suspected congenital long QT syndrome
  - iii) Any history of significant ventricular arrhythmias for example ventricular tachycardia (BT), ventricular fibrillation (VF), and Torsade de Points (TdP).
  - iv) prolonged QTc interval on pre-entry electrocardiogram that is considered clinically significant according to investigator's criteria
  - v) Any history of second- or third-degree heart block (may be eligible if the subject currently has a pacemaker)
  - vi) Not applicable per Amendment 02
  - vii) Not applicable per Amendment 02
  - viii) Not applicable per Amendment 02
- d) Not applicable per Amendment 02
- e) Subjects with prior history of pericardial effusion or pleural effusion that required thoracentesis are excluded. Subjects with prior history of pericardial or pleural effusion that was clinically manageable and a maintained CMR for  $\geq 1$  year on a stable dose of dasatinib are allowed.

- f) History of significant bleeding disorder unrelated to CML, including
  - i) Diagnosed congenital bleeding disorders (e.g., von Willebrand's disease)
  - ii) Diagnosed acquired bleeding disorder within one year (e.g., acquired anti-factor VIII antibodies)

### **3. Physical and Laboratory Test Findings**

- a) Not applicable per Amendment 02.

### **4. Allergies and Adverse Drug Reaction**

- a) Subjects with known hypersensitivity to excipients of dasatinib tablets (Tablet core: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium; hydroxypropyl cellulose, magnesium stearate; Film-coating: hypromellose titanium dioxide macrogol 400).

### **5. Sex and Reproductive Status**

- a) Patients who are pregnant or breastfeeding or likely to become pregnant
- b) Men whose partner is unwilling or unable to avoid pregnancy.

### **6. Other Exclusion Criteria**

- a) Patients with a history of non-compliance to CML treatment and monitoring requirements
- b) Prisoners or subjects who are involuntarily incarcerated
- c) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

### **7. Additional Criteria for Patients Eligible to Re-start Dasatinib**

- a) Any patient who has lost MMR and is eligible for re-starting dasatinib therapy must not have developed a condition that precludes dasatinib use, e.g., pulmonary arterial hypertension. Such a subject will be dropped from treatment with dasatinib and treated according to the investigator's choice.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

#### **3.3.3 Women of Childbearing Potential**

A women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, women under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.\*

\*Women treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of

the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is >40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months.

### **3.4 Concomitant Treatments**

The prohibited and restricted treatment sections are applicable throughout any period when dasatinib is prescribed, i.e., during screening and during the restart of dasatinib when the study drug will be administered until the end of the study.

#### **3.4.1 Prohibited and/or Restricted Treatments**

The following treatments are prohibited throughout any period when dasatinib is prescribed, ie, during screening and during the restart of dasatinib when the study drug will be administered until the end of the study.

Medications associated with QT interval prolongation that are prohibited in this study include:

- quinidine, procainamide, disopyramide
- amiodarone, sotalol, ibutilide, dofetilide
- erythromycins, clarithromycin
- chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide
- cisapride, bepridil, droperidol, methadone, arsenic, chloroquine, domperidone, halofantrine, levomethadyl, pentamidine, sparfloxacin, lidoflazine.

#### **3.4.2 Other Restrictions and Precautions**

**The following restrictions and precautions apply throughout any period when dasatinib is prescribed i.e., during screening and during the restart of dasatinib when the study drug will be administered until the end of the study.**

Caution should be exercised if subjects are required to take medications that inhibit platelet function or anticoagulants. Antiplatelet agents or anticoagulants should be avoided in the setting of Grade 3 or 4 thrombocytopenia.

Ideally, subjects should not be taking other medications known to prolong the QT interval. A partial list of medications known to prolong the QT interval is found in [Appendix 3](#). However, should the investigator believe that therapy with a potentially QT prolonging medication (other than the ones explicitly prohibited) is vital to an individual subject's care, then additional ECG(s) will be done at the investigator's discretion to ensure the subject's safety.

Caution is warranted when administering dasatinib to subjects taking drugs that are highly dependent on CYP3A4 for metabolism and have a narrow therapeutic index. See [Appendix 4](#) for

a list of common CYP3A4 substrates. Systemic exposures to these medications could be increased while receiving dasatinib.<sup>21</sup>

Additionally, strong to moderate CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, erythromycin, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin) may significantly increase concentrations of dasatinib and should be used with caution when administered concurrently with dasatinib or imatinib. Strong to moderate CYP3A4 inducers (eg, rifampicin) may decrease the concentration of dasatinib and should be used with caution when administered concurrently with dasatinib or imatinib. See [Appendix 5](#) and [Appendix 6](#) for a list of CYP3A4 inhibitors and inducers respectively.

In vitro solubility data indicate that dasatinib may have decreased solubility and absorption at pH > 4. Until further data are available, subjects should try to avoid taking proton pump inhibitors and H<sub>2</sub> antagonists. Short-acting antacid agents (eg, aluminum or magnesium hydroxide, calcium carbonate) may be taken, but it is recommended that these not be taken 2 hours before or 2 hours after dosing of dasatinib.

Based on pre-clinical data, dasatinib might increase the likelihood of bleeding. Hence, subjects undergoing surgical procedures, including dental procedures should be instructed to inform their doctors of this potential increased risk

#### **Hematopoietic Growth Factors:**

The use of G-CSF, GM-CSF, erythropoietin or darbepoetin is allowed in this study.

### **3.5 Discontinuation of Subjects from Treatment or from Study**

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment, or to be withdrawn from study while off therapy
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness.

All subjects who discontinue investigational product should comply with protocol specified follow-up procedures as outlined in [Section 5](#). The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study treatment is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

### **3.6 Post Treatment Study Follow up**

In this study, overall survival is a key endpoint of the study. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue the study must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with [Section 5](#) Study Procedures and Assessments until death or the conclusion of the study.

#### **3.6.1 Withdrawal of Consent**

Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

#### **3.6.2 Lost to Follow-Up**

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

## **4. TREATMENTS**

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 4.1](#) for product description.

## 4.1 Study Treatments

**Table 4.1-1: Product Description**

<b>Product Description and Dosage Form</b>	<b>Potency</b>	<b>Primary Packaging (Volume)/ Label Type</b>	<b>Secondary Packaging (Qty) /Label Type</b>	<b>Appearance</b>	<b>Storage Conditions (per label)</b>
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

#### **4.1.1 Investigational Product**

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational product(s) is dasatinib.

#### **4.1.2 Non-investigational Product**

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

This protocol does not include non-investigational products.

#### **4.1.3 Handling and Dispensing**

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

For non-investigational product, if marketed product is utilized, it should be stored in accordance with the package insert, summary of product characteristics (SmPC), or similar.

### **4.2 Method of Assigning Subject Identification**

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

### **4.3 Selection and Timing of Dose for Each Subject**

For all patients enrolled in the study, dasatinib will be discontinued upon study entry.

Patients will be closely monitored for maintenance of MMR (BCR-ABL transcripts < 0.1% on International Scale) after dasatinib withdrawal. In 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 entry.

A rise of PCR > 0.0032% (4.5 log reduction on IS) during the treatment discontinuation period should not trigger a dasatinib re-initiation, as long as the BCR-ABL transcripts remain below 0.1% on IS.

#### **4.3.1 Dose Adjustments**

Dasatinib dose adjustments are allowed during the restart of treatment with the study drug for patients losing MMR.

Dose adjustments for response and toxicity are permitted as presented in Table 4.3.1-1.

**Table 4.3.1-1: Dose Modification Levels**

<b>Dose Level</b>	<b>Dasatinib</b>
Escalation (+2)	180 mg daily
Escalation (+1)	140 mg daily
Labeled Dose	100 mg daily
Reduction (-1)	80 mg daily
Reduction (-2)	50 mg daily

In subjects for whom the dose has been reduced to 80 mg QD of dasatinib after dasatinib restart due to hematologic or non-hematologic toxicities as described below, the dose of dasatinib should be re-escalated to 100 mg QD, if at least 1 month after the dose reduction the following occurs: (a) there are no Grade 3/4 hematologic toxicities, (b) there is no recurrence of the toxicity which led to the dose reduction, and (c) there are no additional  $\geq$  Grade 2 non-hematologic toxicities.

##### **4.3.1.1 Dose Escalation**

Dasatinib may be increased to 140 mg QD during the retreatment period provided that (a) there are no Grade 3 or Grade 4 hematologic toxicities (b) there are no additional  $\geq$  Grade 2 non-hematologic toxicities. Dosing above 180 mg QD of dasatinib is prohibited.

##### **4.3.1.2 Dose Reduction Guidelines**

The dose reduction guidelines for dasatinib are summarized in Table [Table 4.3.1.2-1](#).

Dose interruptions or reductions for dasatinib related adverse events occurring on study during the retreatment period are described in Table 4.3.1.2-1. For an individual subject, dose interruptions, reductions and treatment discontinuation may be more or less conservative than indicated below, based on the clinical judgment of the investigator.

Dasatinib doses below 50 mg are not recommended in this protocol, unless considered by the investigator to be in the best interest of the subject.



**Table 4.3.1.2-1: Summary of Dose Reduction Guidelines**

<b>Dasatinib</b>	
<b>Hematologic</b>	
<b>Grade 1/2</b>	No Dose Interruption/Reduction
<b>Grade ≥ 3 ANC and/or platelets*</b>	Hold therapy Resume @ 100 mg after recovery to ≤ Gr1
	<u>If recurrence</u> Hold therapy Resume @ 80 mg after recovery to ≤ Gr1
	<u>If recurrence @ 80</u> Hold therapy Re-challenge @ 80 mg after recovery to ≤ Gr1
	<u>If recurrence after re-challenge</u> Reduction to 50 mg is required
<b>Non-hematologic</b>	
<b>Grade 2</b>	Hold therapy Resume @ 100 mg after recovery to ≤ Gr1
	<u>If recurrence @ 100</u> Hold therapy Resume @ 80 mg after recovery to ≤ Gr1
	<u>If recurrence @ 80</u> Reduction to 50 mg is required
	<u>If recurrence @ 50</u> Consider treatment discontinuation
<b>Grade ≥ 3</b>	Hold therapy Resume @ 80 mg after recovery to ≤ Gr1
	<u>If recurrence @ 80</u> Hold therapy Resume at 50 mg after recover to ≤ Gr 1
	<u>If recurrence @ 50</u> Consider treatment discontinuation

**Table 4.3.1.2-1: Summary of Dose Reduction Guidelines**

<b>Dasatinib</b>	
<b>Febrile Neutropenia</b>	
<b>≥ Gr3 neutropenia with Temp ≥ 38.5°C (101.3°F)</b>	<p>Hold therapy Initiate appropriate treatment until ANC ≥ 1,000/mm<sup>3</sup> and temperature &lt; 38°C (100.4°F). Resume @ 80 mg</p> <p><u>If recurrence @ 80</u> Dose reduction to 50 mg is required</p> <p><u>If recurrence @ 50</u> Treating physician must judge whether to rechallenge @ 50 <b>OR</b> discontinue treatment due to intolerance.</p>
<b>Liver Function Tests</b>	
<b>Bilirubin &gt; 3x institutional ULN</b>	Hold until bilirubin levels have returned to a < 1.5 x institutional ULN. Resume @ 80 mg
<b>AST/ALT &gt; 5x institutional ULN</b>	Hold until AST/ALT levels have returned to < 2.5 x institutional ULN. Resume @ 80 mg
<b>Bleeding</b>	
	Subjects who have evidence of bleeding or hemorrhage of any grade at any site may have dose adjustments or interruption at the discretion of the investigator
<b>≥ Gr3 anemia/ lymphopenia</b>	<p>No dose reductions.</p> <p>Subjects developing anemia may be transfused or prescribed erythropoietin at the investigator's discretion.</p>

PAH (pre-capillary pulmonary arterial hypertension confirmed by right heart catheterization) has rarely been reported in association with dasatinib treatment as a late event (median onset 29 months (range 8-75)). Patients who develop dyspnea and fatigue after initiation of dasatinib should be evaluated for common causes. In accordance with recommendations for management of non-hematologic adverse reactions, the dose of dasatinib should be reduced or therapy interrupted during this evaluation. If no explanation is found, or if there is no improvement with dose reduction or interruption, a diagnosis of PAH should be considered and guidance from a cardiopulmonary physician sought if necessary. The diagnostic approach and follow up should follow locally applicable, standard practice guidelines including specialist referral, if country practice requires it. If PAH is confirmed, dasatinib should be permanently discontinued.

#### **4.4 Blinding/Unblinding**

Not applicable.

## **4.5 Treatment Compliance**

When treatment with dasatinib is restarted, compliance will be monitored by drug accountability (pill count), as well as recording study drug administration in the subject's medical record and CRF.

## **4.6 Destruction and Return of Study Drug**

### **4.6.1 Destruction of Study Drug**

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

### **4.6.2 Return of Study Drug**

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible BMS Study Monitor.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

#### **4.7 Retained Samples for Bioavailability / Bioequivalence**

At the time of receipt of the investigational product by the investigator, BMS will specify the appropriate number of containers or units to select for retention, the conditions of sample storage, the required duration of sample retention, and provisions for returning or disposing of the investigational product. When samples are selected, containers or units should be placed in packaging with a tamper evident seal provided by BMS. Package labeling should clearly identify the contents as bioavailability/bioequivalence (BA/BE) samples and state that the investigational product should be stored in the restricted area with limited access.

## 5. STUDY ASSESSMENTS AND PROCEDURES

### 5.1 Flow Chart/Time and Events Schedule

**Table 5.1-1: Screening and Baseline Assessments**

Procedure	Screening 1	Screening 2	Visit 1 (Baseline)	Notes
				<ul style="list-style-type: none"><li>Visit 1 window is open until all entry criteria are satisfied unless otherwise specified.</li><li>Screening 2: 90 days ± 10 days after Screening 1.</li></ul>
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 <a href="#">Section 5.3</a> 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 <a href="#">Section 3.3.1</a> and <a href="#">Appendix 8</a> 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	

**Table 5.1-1: Screening and Baseline Assessments**

Procedure	Screening 1	Screening 2	Visit 1 (Baseline)	Notes
				<ul style="list-style-type: none"> <li>Visit 1 window is open until all entry criteria are satisfied unless otherwise specified.</li> <li>Screening 2: 90 days <math>\pm</math> 10 days after Screening 1.</li> </ul>
Adverse event assessment			X	
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.
<b>Efficacy-related Laboratory tests</b>				
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).
<b>Patient-reported Outcomes</b>				
(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

**Table 5.1-1: Screening and Baseline Assessments**

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

**Table 5.1-2: On study Assessment: Off Treatment (Dasatinib Discontinued) Assessments**

Procedure	Off Treatment <sup>a,b</sup>	Notes
<ul style="list-style-type: none"> <li>Visit window is <math>\pm 10</math> days for assessment every 3 or 6 months. <math>\pm 5</math> days for monthly assessments.</li> <li>Assessments will continue throughout the 5 year study period.</li> </ul>		
<b>Safety Assessments</b>		
Physical Examination, vital signs and Performance Status (PS)	Every 3 months	
Assessment of signs and symptoms	Every 3 Months	
Adverse event assessment	Every 3 Months	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 $\leq 1$ , stabilize, or are deemed irreversible.
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.	HBV serology test results must be recorded in the CRF. See <a href="#">Section 5.3</a> for recommendations for subjects with positive HBV serology.
Chest X-ray	As clinically indicated	
Pregnancy test	X	One month after discontinuation of dasatinib.
Review Contraception Requirements	X	Review contraception requirements presented in <a href="#">Section 3.3.1</a> and <a href="#">Appendix 8</a> with both WOCBP and male subjects



**Table 5.1-2: On study Assessment: Off Treatment (Dasatinib Discontinued) Assessments**

Procedure	Off Treatment <sup>a,b</sup>	Notes
<b>Efficacy Assessments</b>		
CBC with diff, platelets	Every 3 months	<ul style="list-style-type: none"> <li>Visit window is <math>\pm 10</math> days for assessment every 3 or 6 months. <math>\pm 5</math> days for monthly assessments.</li> <li>Assessments will continue throughout the 5 year study period.</li> </ul>
Cytogenetics	At loss of MMR. <sup>b</sup>	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 <sup>3</sup>
Molecular analysis/Q-PCR	Year 1: Monthly Year 2-5: Every 3 months (see note for exceptions)	<p>Q-PCR analyses to be performed in a centralized lab and expressed in International Scale units</p> <p>Exceptions to Years 2-5, 3 monthly assessment</p> <ul style="list-style-type: none"> <li>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.</li> </ul>
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 5.1-2: On study Assessment: Off Treatment (Dasatinib Discontinued) Assessments**

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

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

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

<sup>b</sup> 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 [Table 5.1-3](#) for study assessments at dasatinib restart and during treatment with dasatinib.

**Table 5.1-3: On Treatment (Dasatinib Restart) Assessments**

Procedure	Restart dasatinib treatment <sup>a,b</sup>	On treatment with dasatinib <sup>b</sup>	End of study visit	Notes
				<ul style="list-style-type: none"><li>Visit window is ± 10 days for assessment every 3 or 6 months. ± 5 days for monthly assessments.</li><li>Assessments will continue throughout the 5-year study period.</li></ul>
Safety Assessments				
Physical Examination, vital signs and Performance Status (PS)	X	Every 3 months	X	
Assessment of signs and symptoms	X	Every 3 months	X	
Adverse event assessment	X	Every 3 months	X	If a pt is taken off tx due to AE, follow-up visits are required q 4 weeks until toxicities resolve to baseline or Grade ≤ 1), stabilize, or are deemed irreversible.
Concomitant medications	X	Every 3 months	X	
ECG	X	As clinically indicated		An ECG will be performed prior to dasatinib restart if ≥ 2 months has elapsed since the most recent ECG
Echocardiogram	X	As clinically indicated		
Serum chemistry	X	Every 3 months and as clinically indicated	X	Within 72 hours prior to restart.
HBV Serology	Only once for subjects not previously tested within 1 year prior to Visit 1.			HBV serology test results must be recorded in the CRF.
Chest X-Ray				See <a href="#">Section 5.3</a> for recommendations for subjects with positive HBV serology.
				As clinically indicated
Pregnancy test	X	Monthly	X	Within 24 hours prior to restart of study drug, and monthly thereafter during the on treatment study periods. During those months when a study visit is not required, a home pregnancy test must be

**Table 5.1-3: On Treatment (Dasatinib Restart) Assessments**

Procedure	Restart dasatinib treatment <sup>a,b</sup>	On treatment with dasatinib <sup>b</sup>	End of study visit	Notes
				<ul style="list-style-type: none"> <li>Visit window is <math>\pm 10</math> days for assessment every 3 or 6 months. <math>\pm 5</math> days for monthly assessments.</li> <li>Assessments will continue throughout the 5-year study period.</li> </ul>
Review Contraception Requirements	X	Every 3 Months	X	<p>performed and the results entered on the Pregnancy Testing Log (<a href="#">Appendix 1</a>). A pregnancy test is required 30 days after the last dose of study drug. A home pregnancy test that is positive for pregnancy must be confirmed at the study site.</p> <p>Review contraception requirements presented in <a href="#">Section 3.3.1</a> and <a href="#">Appendix 8</a> with both WOCBP and male subjects at restart, every 3 months, and at the end of study visit.</p>
<b>Efficacy Assessments</b>				.
CBC with diff, platelets	X	Weekly: Month 1 and 2 after restart Monthly thereafter	X	<p>During the retreatment period, CBC will be performed weekly during the first two months after restart and then monthly thereafter or as clinically indicated. Additional office visits are not required; results are assessed by the investigator according to dasatinib labeling recommendations. Results do not require entry into the study database, unless an abnormal result requires adverse event reporting</p>

**Table 5.1-3: On Treatment (Dasatinib Restart) Assessments**

Procedure	Restart dasatinib treatment <sup>a,b</sup>	On treatment with dasatinib <sup>b</sup>	End of study visit	Notes
				<ul style="list-style-type: none"> <li>Visit window is <math>\pm 10</math> days for assessment every 3 or 6 months. <math>\pm 5</math> days for monthly assessments.</li> <li>Assessments will continue throughout the 5-year study period.</li> </ul>
Cytogenetics	At the loss of MMR			<p>Bone marrow aspirate/biopsy or peripheral blood (FISH) will be performed within 4 weeks of loss of MMR</p> <p>For adequate cytogenetic results, bone marrow (BM) or peripheral blood (FISH) should ideally be performed when the ANC &gt; 500/mm<sup>3</sup></p> <p>Every 6 months until MMR has been regained, yearly thereafter.</p> <p>If CCyR is not maintained, every 6 months</p>
Molecular analysis/ Q-PCR	X	Monthly for the first 3 months, then every 3 months thereafter	X	Q-PCR analyses to be performed in a centralized lab and expressed in International Scale units
	X	See Note	X	Mutational analysis must be done at loss of MMR and/or failure to respond to dasatinib re-introduction or transformation to an advanced phase. Samples to be drawn and stored for future exploratory analysis.
Mutational analysis				
<b>Patient-reported outcomes</b>				
(MDASI) CML symptom burden assessment	At loss of MMR	Every 3 months	X	<p>Patient must complete the PROs during the study visit: at the beginning of the visit is preferred.</p> <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>
EORTC-QLC-C30	At loss of MMR	Every 3 months	X	
<b>Health Care Resource Utilization Assessment</b>	X	Every 3 months	X	

**Table 5.1-3: On Treatment (Dasatinib Restart) Assessments**

Procedure	Restart dasatinib treatment <sup>a,b</sup>	On treatment with dasatinib <sup>b</sup>	End of study visit	Notes
				<ul style="list-style-type: none"><li>• Visit window is ± 10 days for assessment every 3 or 6 months. ± 5 days for monthly assessments.</li><li>• Assessments will continue throughout the 5-year study period.</li></ul>
Clinical drug supplies				
Dispense Study Drug	X	X		Every 3 months until dasatinib treatment stops.

MMR = major molecular response; CCyR = complete cytogenic response; CMR= complete molecular response (MR4.5)<sup>7</sup> Month - 30 days

<sup>a</sup> During the restart period, each assessment is counted from the day dasatinib treatment is restarted after the loss of MMR.

<sup>b</sup> All 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. Dasatinib will be continued for as long as the subject derives clinical benefit from the treatment or until the end of the study..

## 5.2 Study Materials

Special study materials that are needed for this trial are a 12-lead ECG machine, centrifuge and a -20°C or -70°C freezer. Home pregnancy tests and Pregnancy Testing Logs will be furnished by the Sponsor.

The current version of the NCI CTCAE guide will be furnished by the sponsor to each site.

## 5.3 Safety Assessments

Safety will be assessed throughout the study at the time points specified in the Flow Chart/Time and Event schedule presented in [Section 5.1](#). Study drug toxicities will be assessed during the treatment periods. Adverse events will be evaluated according to the current version of the NCI CTCAE guide.

Baseline and on study safety assessments as described below include: physical examination, vital signs and performance Status (PS); assessment of signs and symptoms; ECG at baseline and if clinically indicated thereafter, echocardiogram (if clinically indicated), serum chemistry, and chest x-ray (if clinically indicated).

At baseline, signs and symptoms present within 2 weeks prior to study entry ie dasatinib discontinuation (regardless of relationship to current disease) will be obtained

Physical examination will include assessment of spleen and liver size by manual palpation, weight, performance status and vital signs. Concomitant medications will be reported. An echocardiogram will be performed if clinically indicated as presented in [Table 5.1-1](#), [Table 5.1-2](#) and [Table 5.1-3](#).

A 12-Lead ECG to determine baseline QTc will be done at baseline (screening) if clinically indicated, and at designated time points as clinically indicated. Additional ECGs will be done at the investigator's discretion to ensure the subject's safety, and in case of non-study drug treatment modifications with a potentially QT prolonging medication (other than the ones explicitly prohibited, refer to [Section 3.4.1](#)).

A 12-Lead ECG and echocardiogram will be conducted at the restart of the study drug if clinically indicated.

The schedules of safety assessments to be conducted, during the off treatment period and in the event that dasatinib treatment is restarted after loss of MMR are presented in [Table 5.1-2](#) and [Table 5.1-3](#).

If a patient is taken off treatment due to an adverse event while on study, follow-up visits will be made at least every 4 weeks until all study related toxicities resolve to baseline (or CTC Grade  $\leq 1$ ), stabilize, or are deemed irreversible.

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

## HBV Serology

Although subjects with acute hepatitis B virus (HBV) infection are excluded, subjects with chronic or resolved hepatitis B infection may be enrolled as long as they meet all other eligibility criteria. Consultation with a physician with expertise in the treatment of HBV is recommended for subjects who test positive for HBV serology. Subjects who are carriers of HBV should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In subjects who develop reactivation of HBV while receiving dasatinib, prompt consultation with a physician with expertise in the treatment of HBV is recommended.

### **5.3.1 Safety endpoints**

Safety will be reported for all enrolled subjects, following discontinuation of dasatinib and during re-start with dasatinib. Adverse events and other symptoms will be graded according to the current version of the NCI CTCAE guide. Number of dose interruptions, dose reductions and treatment discontinuations for drug-related toxicity will be analyzed.

## **5.4 Efficacy Assessments**

Efficacy will be assessed throughout the study at the time points specified in the Flow chart/time and event schedule presented in [Section 5.1](#).

Baseline, off-treatment and restart assessments for the determination of efficacy include CBC with differential and PLT count, cytogenetics, and molecular analysis/Q-PCR.

Samples for mutational analysis will be drawn at baseline, and at the time of loss of MMR or any response failure as determined by other planned assessments, and as specified in the time and events schedule. Samples for mutational analysis will be drawn and stored for future exploratory analysis.

### **5.4.1 Efficacy Endpoints**

Efficacy endpoints will be based on cytogenetic and molecular (Q-PCR performed in a centralized lab and expressed in IS) assessments at predefined intervals as specified in [Table 5.1-1](#) to [Table 5.1-3](#).

#### **5.4.1.1 Definition of Hematologic Response**

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

- $WBC \leq 10,000/mm^3$
- Platelets  $<450,000/mm^3$
- 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).



#### **5.4.1.2 Definition of Cytogenetic Response**

Cytogenetic response (CyR) is based on the prevalence of Ph<sup>+</sup> cells in metaphase from bone marrow (BM) sample. Ideally, 25 metaphases but at least 20 metaphases from a BM sample should be evaluated.<sup>22</sup>

The criteria for evaluation of CyR are as follows:<sup>22</sup>

Complete Cytogenetic Response (CCyR): 0% Ph<sup>+</sup> cells in metaphase in BM

Partial Cytogenetic Response (PCyR): 1 to 35% Ph<sup>+</sup> cells in metaphase in BM<sup>22</sup>

Minor Cytogenetic Response: 36 to 65% Ph<sup>+</sup> cells in metaphase in BM

Minimal Cytogenetic Response: 66 to 95% Ph<sup>+</sup> cells in metaphase in BM

No Cytogenetic Response: 96 to 100% Ph<sup>+</sup> cells in metaphase in BM

Major Cytogenetic Response (MCyR) is defined as CCyR plus PCyR

For the assessment of CCyR, FISH of blood interphase cell nuclei can substitute for bone marrow cell metaphases. CCyR is then defined by < 1% BCR-ABL1–positive nuclei of at least 200 nuclei.<sup>13,14,23</sup>

#### **5.4.1.3 Definition of Molecular Response**

Molecular response 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).

A major molecular response (MMR) is defined as BCR-ABL transcripts < 0.1% IS.<sup>13</sup>

CMR is defined as  $\leq 0.0032\%$  or  $\geq 4.5$  log reduction of BCR-ABL transcript levels MR<sup>4,5</sup>. The rate of MMR is defined as the proportion of subjects who maintain MMR (BCR-ABL transcripts < 0.1% (IS)) 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.

#### **5.4.1.4 Event-free survival**

Event free survival is defined as the time from the date of dasatinib treatment discontinuation to the date of loss of MMR. Patients who do not lose MMR will be censored on the date of their last molecular assessment.

#### **5.4.1.5 Relapse (during off treatment period)**

Relapse is defined as any of the following events while a subject is on study: the loss of MMR, CCyR, 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. Patients who do not relapse will be censored on the date of their last molecular assessment.

#### **5.4.1.6 Progression free survival**

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

#### **5.4.2 Progression**

Any of the following events occurring while a subject is in the study, define progression.<sup>13,24</sup>

Progression is defined as Transformation to Accelerated Phase or Blast Crisis (AP/BC)

##### 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)

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.

#### **5.4.3 Overall Survival**

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.

#### **5.5 Pharmacokinetic Assessments**

Not applicable.

#### **5.6 Biomarker Assessments**

Not applicable.

#### **5.7 Outcomes Research Assessments**

[REDACTED]

[REDACTED]

## **5.8 Other Assessments**

Hematology tests will be done to assess the subject's safety and hematologic response. Serum chemistry tests and pregnancy tests will be done to assess the subject's safety.

Bone marrow aspirates and/or biopsies or peripheral blood (FISH) will be performed to monitor the subject's response after restarting dasatinib therapy.

Other parameters and/or increased frequency of examinations may be needed depending on the findings during the study. If a subject experiences an adverse event of pleural effusion and a thoracentesis is performed, the results of the pleural fluid analysis must be recorded on the CRF.

An exploratory analysis identifying prognostic factors will be conducted including age, gender, Sokal risk group, time from diagnosis (months), time (months) in dasatinib-induced stable CMR (MR4.5) prior to discontinuation, occurrence of BCR-ABL blips, history of pleural effusion, and history of lymphocytosis (lymphocytes  $> 3.6 \times 10^9/L^{27,28}$ ). BCR ABL blips are any changes in residual level that do not have clinical relevance and does not imply loss of MMR.

### **5.8.1 Hematology**

CBC, differential and PLT will be obtained within 72 hours prior to enrollment and as indicated on the Time and Events Schedule.

For patients who are returned to treatment with dasatinib, CBC will be performed weekly during the first two months after restart and then monthly thereafter or as clinically indicated. Additional office visits are not required; results are assessed by the investigator according to dasatinib labeling recommendations. Results do not require entry into the study database, unless an abnormal result requires adverse event reporting.

### **5.8.2 Serum chemistry Tests**

BUN, creatinine, ALT, AST, alkaline phosphatase, total bilirubin, LDH, Na, K, Mg, P, total serum or ionized Ca and uric acid will be obtained within 72 hours prior to enrollment and as indicated on the Time and Events schedule.

Only tests listed above are required to be collected and reported in the CRF.

### **5.8.3 Bone Marrow/Peripheral Blood (FISH).**

Bone marrow aspirates and/or biopsies or peripheral blood (FISH) will be performed for subjects at the loss of MMR by Q-PCR assessment.

### **5.8.4 Molecular Analysis**

Q-PCR analyses to be performed in a centralized lab and expressed in International Scale units.

Patients in CMR with detectable BCR-ABL will be assessed monthly for the first year and every 3 months thereafter.

As defined in [Section 5.8](#), BCR-ABL blips are any increases in BCR-ABL level that do not have clinical relevance (return to or below baseline without change in treatment and do not indicate loss of MMR).

### **5.8.5 Pregnancy Test**

For women of child-bearing potential, a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of  $\beta$ HCG) is required at screening and 30 days after treatment discontinuation.

If the dasatinib is restarted, a serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of  $\beta$ HCG) is required within 24 hours prior to restart, and monthly thereafter, and at the end of the study. A pregnancy test is required 30 days after the last dose of study drug.

Home pregnancy tests, furnished by the Sponsor, will be distributed to WOCBP along with the Pregnancy Testing Log ([Appendix 1](#)). Patients are required to bring the log to each study visit. Pregnancy Testing Log data will be entered into the CRF. A home pregnancy test that is positive for pregnancy must be confirmed at the study site.

## **5.9 Results of Central Assessments**

Q-PCR assessments will be performed in a central laboratory and results will be communicated to the investigator site on regular bases (e.g., within 2-3 weeks).

## 6. ADVERSE EVENTS

An **Adverse Event (AE)** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

### 6.1 Serious Adverse Events

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see [NOTE](#) below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See [Section 6.6](#) for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 6.1.1 for reporting details).

**NOTE:**

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

### **6.1.1      *Serious Adverse Event Collection and Reporting***

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing. The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). When using paper forms, the reports are to be transmitted via email or confirmed facsimile (fax) transmission to:

**SAE Email Address:** See Contact Information list.

**SAE Facsimile Number:** See Contact Information list.

For studies capturing SAEs/pregnancies through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted

immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

**SAE Telephone Contact** (required for SAE and pregnancy reporting): See Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

## **6.2 Nonserious Adverse Events**

A *nonserious adverse event* is an AE not classified as serious.

### **6.2.1 Nonserious Adverse Event Collection and Reporting**

The collection of nonserious AE information should begin at enrollment.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see [Section 6.1.1](#)). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

## **6.3 Laboratory Test Result Abnormalities**

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

## **6.4 Pregnancy**

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance

Form to BMS (or designee) within 24 hours and in accordance with the SAE reporting procedures described in [Section 6.1.1](#).

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug, after a thorough discussion of benefits and risk with the subject.

Protocol required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and where applicable, offspring information must be reported on the Pregnancy Surveillance form

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

## **6.5 Overdose**

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details).

## **6.6 Potential Drug Induced Liver Injury (DILI)**

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as:

1. AT (ALT or AST) elevation  $> 3$  times upper limit of normal (ULN)

AND

2. Total bilirubin  $> 2$  times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

AND

3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

## **6.7 Other Safety Considerations**

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.



## **7. DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES**

An external steering committee composed of clinicians who treat patients with CML-CP have been consulted throughout the development of the protocol and will participate in data analysis and interpretation.

In addition, 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 would have the remit of regularly assessing study progress at defined intervals (at least 2 times a year and ad-hoc as necessary), reviewing safety data including all SAEs, grade 3 and 4 AEs and discontinuations and examining critical efficacy endpoints (e.g. MMR, CCyR and disease progression) of the study.

## **8. STATISTICAL CONSIDERATIONS**

### **8.1 Sample Size Determination**

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 subjects will be enrolled into this trial.

### **8.2 Populations for Analyses**

- Enrolled subjects: All subjects who signed an informed consent.
- Evaluable subjects: All enrolled subjects who do not have any major deviations or violations of the protocol.
- All enrolled subjects 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 the enrolled and evaluable subject populations. Safety, extent of exposure, and health outcome will be tabulated and analyzed for the enrolled subjects.

### **8.3 Endpoints**

#### **8.3.1 Primary Endpoint(s)**

The primary efficacy endpoint is the proportion of subjects who maintain MMR at 12 months after dasatinib discontinuation without re-starting dasatinib treatment in the enrolled subjects in the study. In addition, the MMR rate will be estimated for the evaluable subjects. Loss of MMR is defined per ELN definition of progression ([Section 5.4.2](#)).<sup>24</sup> In the event that any subject discontinues the study or dies prior to 12 months then these events will be considered failures and these patients will be included in the denominator of the proportion, following the intent to treat principle.

### **8.3.2 Secondary Endpoint(s)**

The secondary efficacy endpoints include

- event-free survival (EFS) (defined as survival with no loss of MMR) at 12, 24, 36, 48 and 60 months after dasatinib discontinuation
- relapse-free survival (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 or less with measurable levels
- the rate of transformation to AP/BC
- PFS
- overall survival (OS)



### **8.3.4 Safety Endpoints**

Safety endpoints include the frequency and CTCAE grade of adverse events during discontinuation of study treatment and during treatment (re-start of dasatinib), the number of dose interruptions, dose reductions and treatment discontinuations for drug-related toxicity.

### **8.3.5 Outcome Research Endpoints**

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.

## **8.4 Analyses**

No formal statistical testing will be performed. Due to the study design, some of the efficacy endpoints usually considered as efficacy will be considered as both efficacy and safety endpoints: progression of disease (per ELN guidelines) which includes transformation to AP/BC and death due to any reason, and risk associated with re-gaining MMR following re-start of dasatinib.

#### **8.4.1 Demographics and Baseline Characteristics**

Summary statistics will be provided for subject disposition and baseline characteristics (demographics, medical history, etc.) using the enrolled subject population.

#### **8.4.2 Efficacy Analyses**

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. The point estimate and Clopper-Pearson two-sided 95% confidence intervals of MMR at 12 months will be summarized. In the event that there are either deaths or study discontinuations prior to 12 months, these will be considered failures and these patients will be included in the denominator of the proportion, following the intent to treat principle risks.

The secondary analysis including time to event endpoints: EFS, RFS, PFS, OS will be analyzed using Kaplan-Meier Methods at yearly intervals. Rates of transformations will be analyzed as binary using Clopper-Pearson methods. 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. Censoring details are provided in the [Section 5.4](#) and will be further specified in the statistical analysis plan (SAP). 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 or less with measurable levels will be summarized by visit and using a spider plot.

An exploratory analysis identifying prognostic factors for maintaining MMR at 12 months after dasatinib discontinuation without re-starting dasatinib including age, gender, Sokal risk group, time from diagnosis, time in dasatinib-induced stable CMR (MR4.5) prior to discontinuation, occurrence of BCR-ABL before loss of remission, history of pleural effusion, and history of lymphocytosis will be conducted. Hazard ratios and 95% confidence intervals and P-values for these factors will be estimated using Cox proportional hazard model. Further details will be included in the SAP. Additional exploratory analyses will include estimating the rates of subjects who achieve molecular re-response (rMMR and rCMR) and cytogenetic re-response (rCCyR and rPCyR) after relapse using Kaplan-Meier method, and analyzing time to re-gaining molecular re-response (rMMR and rCMR) and cytogenetic re-response (rCCyR and rPCyR) after relapse using Kaplan-Meier and Brookmeyer-Crowley methods.

#### **8.4.3 Safety Analyses**

All safety data will be summarized using the enrolled subjects population. Frequency and CTCAE grading of adverse events will be summarized during off-treatment (upon discontinuation of study treatment) and retreatment study periods. Number of dose interruptions, dose reductions and treatment discontinuations for drug-related toxicity will also be summarized. Physical examination, vital signs and performance status, assessment of signs and symptoms, ECG, echocardiogram, serum chemistry, and chest x-ray will be summarized by visit.

#### **8.4.4 Pharmacokinetic Analyses**

Not applicable.

#### **8.4.5 Biomarker Analyses**

Not applicable.

#### **8.4.7 Other Analyses**

Not applicable.

### **8.5 Interim Analyses**

The Sponsor will conduct continuous review and reporting of safety throughout the study as required by GCP and routine pharmacovigilance standards.

In case of any progression from chronic phase to accelerated phase or blast crisis during the discontinuation phase, the steering committee and the internal data monitoring committee will be consulted and the case will be discussed to decide potential early study termination.

An interim analysis is planned when all patients have been followed until month 12 (calculated from discontinuation of dasatinib). This analysis will assess specific safety and efficacy endpoints and will be detailed in the statistical analysis plan.

Regular reviews (at least 2 times a year and ad-hoc as necessary) 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.

## **9. STUDY MANAGEMENT**

### **9.1 Compliance**

#### **9.1.1 Compliance with the Protocol and Protocol Revisions**

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion

- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

### **9.1.2 Monitoring**

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

### **9.1.3 Investigational Site Training**

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

## **9.2 Records**

### **9.2.1 Records Retention**

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

### **9.2.2 Study Drug Records**

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by BMS) is maintained at each study site where study drug is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

### **9.2.3 Case Report Forms**

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and

approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

### **9.3 Clinical Study Report and Publications**

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected considering the following criteria:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

## 10. GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or BMS as related to the investigational product
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)
Serious Adverse Event	Serious adverse event defined as any untoward medical occurrence that at any dose: results in death; is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe), requires inpatient hospitalization or causes prolongation of existing hospitalization; results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect; is an important medical event (defined as a medical event(s) that may not be immediately life threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.). For reporting purposes only, BMS also considers the occurrence of pregnancy, overdose (regardless of association with an AE), and cancer as important medical events.



## 11. LIST OF ABBREVIATIONS

Term	Definition
ALL	Acute Lymphoblastic Leukemia
AE(s)	Adverse Events(s)
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Accelerated Phase
Ara-C	Cytosine Arabinoside
AST	Aspartate aminotransferase
ATP	Adenosine Triphosphate
BC	Blast Crisis
BCR-ABL blips	BCR-ABL kinetics in subjects who experience intermittent loss of CMR (MR4.5) but no loss of MMR
BID	Bis In Diem (twice a day)
BM	Bone Marrow
BMS	Bristol-Myers Squibb
BP	Blast Phase
BUN	Blood Urea Nitrogen
Ca	Calcium
CBC	Complete Blood Count
CHR	Complete Hematologic Response
cCHR	Confirmed Complete Hematological Response
CCyR	Complete Cytogenetic Response
CyR	Cytogenetic Response
CI	Confidence Interval
CML	Chronic Myeloid Leukemia
CMR	Complete Molecular Response
CNS	Central Nervous System
CP	Chronic phase
CRF	Case Report Form
CSF	Cerebro Spinal Fluid
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P
ECG	Electrocardiogram
ECOG	Eastern Co-Operative Group
EFS	Event-free survival
eg	Exempli Gratia (for example)
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
ESR	Expedited Safety Report

Term	Definition
FSH	Follicle Stimulating Hormone
FISH	Fluorescent-In Situ Hybridization
GCP	Good Clinical Practice
GI	Gastrointestinal
HCG	Human Chorionic Gonadotropin
HRT	Hormone Replacement Therapy
HU	Hydroxyurea
ICH	International Conference on Harmonization
IDMC	Internal Data Monitoring Committee
ie	Id Est (that is)
IEC	Independent Ethics Committee
IM	Imatinib mesylate
$\alpha$ -IFN	Interferon- $\alpha$
INR	International Normalized Ratio
IRB	Institutional Review Board
IS	International Scale
IU	International Unit
IV	Intravenous
K	Kalium (Potassium)
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
MCyR	Major Cytogenetic Response
mg	Milligram
Mg	Magnesium
$\mu$ M	microMolar
MMR	Major Molecular Response
MR	Molecular response
MR <sup>4.5</sup>	$\leq 0.0032\%$ (IS) or 4.5 log reduction of BCR-ABL transcript as determined by local standards
Msec	Millisecond
N	Number (of subjects or observations)
Na	Natrium (Sodium)
NCI	National Cancer Institute
nM	nanoMolar
OS	Overall Survival
P	Phosphorus
PB	Peripheral Blood
PCR	Polymerase Chain Reaction
PCyR	Partial Cytogenetic Response
PDGF	Platelet-Derived Growth Factor

<b>Term</b>	<b>Definition</b>
PFS	Progression-Free Survival
pH	$-\log_{10}$ Hydrogen Ion Concentration
Ph+	Philadelphia Chromosome Positive
PLT	Platelets
p.o.	Per os (by mouth)
PS	Performance Status
PTK	Protein Tyrosine Kinase
Q	Every
QD	once daily
QT	The interval between the beginning of the Q-wave and the end of the T-wave on an electrocardiogram
QTc(F)	QT Interval Corrected (according to Fridericia's formula)
rCMR	Re-attainment of Complete Molecular Response after relapse
rMMR	Re-attainment of Major Molecular Response after relapse
RQ-PCR	Real-time Quantitative Polymerase Chain Reaction
SAE	Serious Adverse Event
SCT	Stem cell transplant
S(m)PC	Summary of Product Characteristics
SOP	Standard Operating Procedures
SRC	a protein tyrosine kinase
ULN	upper limit of normal
WBC	White Blood Cell
WOCBP	Women of Child Bearing Potential







## APPENDIX 1 PREGNANCY TESTING LOG

<b>Subject Identifier:</b>	<b>Protocol Number: CA180-406</b>
<b>Investigator:</b>	<b>Site Number:</b>
<b>Beginning Date:</b>	<b>End Date:</b>

*Please fill in the information monthly and bring the log to your doctor visits*

Month (Jan, Feb, ...)	Was the test performed? (Circle)	Date of Test Day / Month / Year	*Test Results (Circle)
	Yes      No		Negative      Positive
	Yes      No		Negative      Positive
	Yes      No		Negative      Positive
	Yes      No		Negative      Positive
	Yes      No		Negative      Positive
	Yes      No		Negative      Positive
	Yes      No		Negative      Positive
	Yes      No		Negative      Positive
	Yes      No		Negative      Positive
	Yes      No		Negative      Positive
	Yes      No		Negative      Positive
	Yes      No		Negative      Positive
	Yes      No		Negative      Positive
	Yes      No		Negative      Positive

**\* IF ANY TEST IS POSITIVE, PLEASE CONTACT YOUR DOCTOR IMMEDIATELY.**

*Please fill in the information monthly and bring the log to your doctor visits*

CA180-406

Property of BMS and Confidential

Page \_\_\_\_ of \_\_\_\_

Revised Protocol No.: 04  
Date: 24-Jul-2017

## **Guidelines of Acceptable Methods of Contraception**

**NOTE:** The wording below is provided as an example and may be revised based on local input and requests, as long as protocol requirements are maintained.

Use of dasatinib during pregnancy can be harmful to the developing fetus (baby), potentially resulting in birth defects or the death of the fetus. At a minimum, you must agree to use two methods of contraception. One method must be highly effective (selected from Section A below) and the second method must be either highly effective or less effective (selected from Section B below):

### **A. HIGHLY EFFECTIVE METHODS OF CONTRACEPTION**

Highly Effective contraception methods are as follows:

1. Progestogen only hormonal contraception associated with inhibition of ovulation.
2. Hormonal methods of contraception including oral contraceptive pills containing combined estrogen + progesterone, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena®
3. Nonhormonal intrauterine devices (IUDs), such as ParaGard®
4. Bilateral tubal occlusion (also known as having tubes tied)
5. Vasectomised partner with documented azoospermia 90 days (test done to show that there is no sperm) after procedure
  - a. Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
  - b. If using this method of contraception, male subjects with partners who are WOCBP must also use condoms.
6. Intrauterine hormone-releasing system (IUS).
7. Complete abstinence
  - a. Complete abstinence is defined as the complete avoidance of heterosexual intercourse.
  - b. Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment plus 31 days.
  - c. It is not necessary to use any other method of contraception when complete abstinence is elected.
  - d. If you choose complete abstinence, you must continue to have pregnancy tests monthly

### **B. LESS EFFECTIVE METHODS OF CONTRACEPTION**

1. Diaphragm with spermicide
2. Cervical cap with spermicide
3. Vaginal sponge with spermicide



4. Male or female condom with or without spermicide\*
5. Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.

\* A male and a female condom must not be used together.

#### **C. UNACCEPTABLE METHODS OF CONTRACEPTION**

1. Periodic abstinence (calendar, symptothermal, post-ovulation methods)
2. Withdrawal (coitus interruptus)
3. Spermicide only
4. Lactation amenorrhea method (LAM)



### **APPENDIX 3      MEDICAL CONDITIONS AND DRUGS WHICH MAY CAUSE QTC PROLONGATION AND TORSADE DE POINTES (NOT ALL INCLUSIVE)**

Refer to <http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists.htm>

Patients are prohibited from taking medications listed in the Known Risk of Torsade de Pointes Category. Caution is warranted when administering BMS-354825 to subjects taking drugs associated with prolongation of QTc listed in Possible Risk of Torsade de Pointes and Conditional Risk of Torsade de Pointes Categories. A separate study document delineating medications currently listed in all risk categories will be provided and updated as necessary.

## **APPENDIX 4      COMMON CYP3A4 SUBSTRATES (NOT ALL INCLUSIVE)**

The following lists describe medications which are common CYP3A4 substrates. This list should not be considered all inclusive. Consult individual drug labels for specific information on a compound's propensity for metabolism by CYP3A4.

### Macrolide Antibiotics:

clarithromycin  
erythromycin  
NOT azithromycin

### Anti-arrhythmics:

quinidine  
Benzodiazepines:  
alprazolam  
diazepam  
midazolam  
triazolam

### Immune Modulators:

cyclosporine  
tacrolimus (FK506)

### HIV Antivirals:

indinavir  
nelfinavir  
ritonavir  
saquinavir

### Antihistamines:

astemizole  
chlorpheniramine  
terfenidine

### Calcium Channel Blockers:

amlodipine  
diltiazem  
felodipine  
lercanidipine  
nifedipine  
nisoldipine  
nitrendipine  
verapamil

### HMG CoA Reductase Inhibitors:

atorvastatin  
cerivastatin

lovastatin  
NOT pravastatin  
Simvastatin

Steroid 6beta-OH:

estradiol  
hydrocortisone  
progesterone  
testosterone

Others:

alfentanil  
buspirone  
cafergot  
caffeine  
cocaine  
dapson  
codeine-N-demethylation  
dextromethorphan  
eplerenone  
fentanyl  
finasteride  
gleevec  
haloperidol  
irinotecan  
LAAM  
lidocaine  
methadone  
odanestron  
pimozide  
propranolol  
quinine  
salmeterol  
sildenafil  
sirolimus  
tamoxifen  
taxol  
terfenadine  
trazodone  
vincristine  
zaleplon  
zolpidem

## APPENDIX 5 COMMON CYP3A4 INHIBITORS (NOT ALL INCLUSIVE)

The following lists describe medications and foods which are strong to moderate inhibitors of CYP3A4. This list should not be considered all inclusive. Consult individual drug labels for specific information on a compound's propensity to inhibit CYP3A4.

**Table App. 5: CYP3A4 Inhibitors**

<b>Strong CYP3A4 Inhibitors</b>	<b>Moderate CYP3A4 Inhibitors</b>	<b>Weak CYP3A4 Inhibitors</b>
≥ 5-fold increase in AUC	≥ 2 but < 5-fold increase in AUC	≥ 1.25 but < 2-fold increase in AUC
atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycins	amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice(a), verapamil	cimetidine

## **APPENDIX 6          COMMON CYP3A4 INDUCERS (NOT ALL INCLUSIVE)**

The following lists describe medications which are common inducers of CYP3A4. This list should not be considered all inclusive. Consult individual drug labels for specific information on a compound's propensity to induce CYP3A4.

### HIV Antivirals:

efavirenz  
nevirapine

### Others:

barbiturates  
carbamazepine  
glucocorticoids  
modafinil  
phenobarbital  
phenytoin  
rifampin  
St. John's wort  
troglitazone  
pioglitazone  
rifabutin





## APPENDIX 8 METHODS OF CONTRACEPTION

At a minimum, women of childbearing potential (WOCBP) and WOCBP who are partners of male subjects must agree to the use of **two methods of contraception**, with one method being highly effective and the other method being either highly effective or less effective as listed below:

### HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol are expected to adhere to using contraception (including condoms as the required second method) with their partner. Contraception methods are as follows:

1. Progestogen only hormonal contraception associated with inhibition of ovulation.
2. Hormonal methods of contraception including oral contraceptive pills containing combined estrogen + progesterone, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena®
3. Nonhormonal IUDs, such as ParaGard®
4. Bilateral tubal occlusion
5. Vasectomised partner with documented azoospermia 90 days after procedure
  - ◆ Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
  - ◆ If using this method of contraception, male subjects with partners who are WOCBP must also use condoms.
6. Intrauterine hormone-releasing system (IUS).
7. Complete abstinence
  - ◆ Complete abstinence is defined as the complete avoidance of heterosexual intercourse. (refer to Glossary of Terms)
  - ◆ Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment (plus 5 half-lives of the investigational drug plus 30 days).
  - ◆ It is not necessary to use any other method of contraception when complete abstinence is elected.
  - ◆ Subjects who choose complete abstinence must continue to have pregnancy tests, as specified in [Section 6.4](#)
  - ◆ Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
  - ◆ The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

### LESS EFFECTIVE METHODS OF CONTRACEPTION

1. Diaphragm with spermicide
2. Cervical cap with spermicide
3. Vaginal sponge with spermicide
4. Male or female condom with or without spermicide\*
5. Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.

\* A male and a female condom must not be used together.

#### **UNACCEPTABLE METHODS OF CONTRACEPTION**

- 1) Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- 2) Withdrawal (coitus interruptus)
- 3) Spermicide only
- 4) Lactation amenorrhea method (LAM)