Official Title of Study:

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

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Date: 09-Apr-2012
Revised Date 09-Mar-2018

Clinical Protocol CA180399

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

Revised Protocol: 07
Incorporates Administrative Letter 03 and 04

Study Director/Central Medical Monitor
Patricia Martín-Regueira, MD Director
[redacted]
6

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 whom BMS has transferred obligations, eg, 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 CA180399

Protocol Title: An open label, randomized (2:1) Phase 2B study of dasatinib vs. imatinib in patients with chronic phase chronic myeloid leukemia who have not achieved an optimal response to 3 months of therapy with 400 mg imatinib

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):

Patients randomized to treatment with dasatinib will be administered dasatinib, orally, at a dose of 100 mg QD. Subjects may adjust the time they take dasatinib as long as they take the drug approximately every 24 hours.

Patients randomized to treatment with imatinib will be administered imatinib, orally, at a dose of ≥ 400 mg QD or BID, depending on the dose chosen. Each dose should be administered with a meal and taken with a large glass of water. Subjects may adjust the time they take imatinib as long as they take the drug every 24 hours for 400 mg and 600 mg dosing or every 12 hours for 400 mg BID dosing, and follow instructions regarding meals.

Subjects will be treated with dasatinib or imatinib until disease progression, treatment failure, unacceptable toxicity, withdrawal of subject's consent, the investigator and the subject feel that it is in the best interest of the subject to discontinue treatment, for reasons outlined in Section 3.5 Discontinuation of Subjects from Treatment, or until a maximum of 60 months from the randomization of the last patient.

Patients randomized to treatment with imatinib who meet ELN 2013 criteria for failure [Appendix 8] will be switched to the treatment with dasatinib.

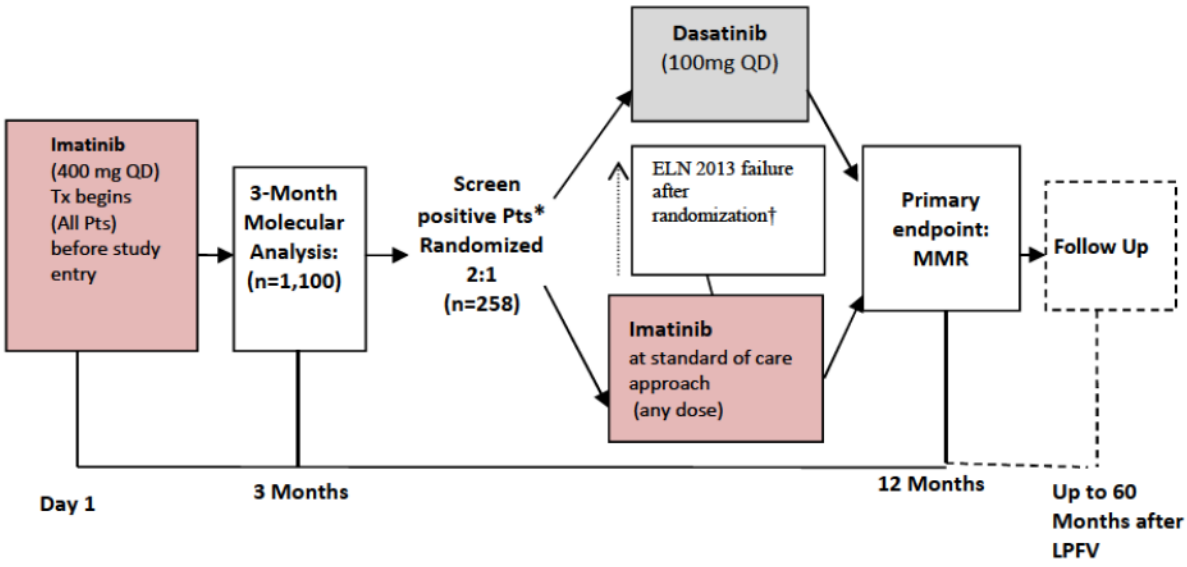
Study Phase: Phase 2b

Research Hypothesis: This study proposes to test the hypothesis that patients with chronic phase chronic myeloid leukemia (CP-CML) with BCR-ABL transcript level >10% IS [International Standard] after 3 months of treatment with first-line imatinib 400mg will achieve a greater rate of major molecular response (MMR) by early switching to dasatinib therapy 100 mg QD compared with continued treatment with imatinib at any dose selected by the investigator.

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

Secondary objectives are to compare the following between both treatment arms: time to MMR; time to MR4.5; Progression-free Survival (PFS); and Overall Survival (OS).

Study Design:



Screen positive patients are those who achieved CHR, but with > 10% IS BCR-ABL at 3 months.
Patients with transcript levels ≤10% IS are screen failures.
†Patients randomized to Imatinib, meeting ELN 2013 failure criteria, [Appendix 8] and without dasatinib resistant mutations (e.g. T315I/A, F317L, V299L) will be crossed over to the dasatinib arm. Crossover patients will begin study assessments specified in Table 5.1B calculated from Day 1 of dasatinib dosing.

LPFV= Last patient, first visit; MMR=major molecular response; QD= once daily; Pts=patients; Tx=treatment.

Randomization will be stratified by:

1) Sokal score: High, Intermediate, Low, or Unknown
2) Time between 3 month molecular assessment and randomization: (≤ 4 weeks vs > 4 weeks)

Study Population: CP-CML Ph+ patients with complete hematologic response (CHR) but with BCR-ABL level > 10% IS after 3 months of imatinib 400 mg treatment. Imatinib monotherapy must have been started within 6 months of CP-CML diagnosis. Patients treated with imatinib preceding the 3-month molecular response assessment are considered the screened population. Screened patients with a transcript level of 10% IS or less after 3 months of imatinib 400 mg treatment are excluded from the study.

Study Assessments:

Safety assessments include: physical examination (including assessment of spleen and liver size, weight, performance status, vital signs, concomitant medications), signs and symptoms, ECG, echocardiogram, serum chemistry and chest x-ray. Adverse events will be assessed throughout this study using NCI CTCAE Version 4.0.

Efficacy assessments include: CBC with differential, platelets, cytogenetics, and molecular analysis (qualitative polymerase chain reaction [Q-PCR]).

The schedule of study assessments is presented in Section 5, Study Assessments and Procedures.

Statistical Considerations:

Sample Size:

This study will test the hypothesis that patients with CP-CML with less than one log BCR-ABL reduction (BCR-ABL > 10% IS) after 3 months of treatment with first-line imatinib 400 mg will achieve a greater rate of MMR by early switching to dasatinib therapy 100 mg QD compared with staying on imatinib at any dose selected by the investigator.

MMR at 12 months after Day 1 initiation of first-line treatment with imatinib, in patients randomized at month 3 to treatment with dasatinib 100mg QD or imatinib at any dose is the primary endpoint in this study. The analysis will require the screening of approximately 860 subjects in order to randomize 258 subjects, 172 in dasatinib group and 86 in imatinib group under the following design assumptions 2:1 (dasatinib, imatinib) randomization ratio, (with randomization occurring no more than 8 weeks after the 3 month molecular analysis) 2-sided superiority test with α=0.05 and 90% power, and MMR at 12 months of 10% for imatinib and 25% for dasatinib.

Endpoints:

The primary endpoint is MMR at 12 months after Day 1 of first-line imatinib in patients randomized at month 3 to treatment with either dasatinib 100 mg QD or imatinib at any dose.

Secondary endpoints are time to MMR, time to molecular response (MR)[4 5] progression free survival (PFS), and overall survival (OS).

[redacted]

Efficacy

All efficacy analyses will be performed on the dataset of 'all randomized subjects' and all comparisons between treatment arms will be carried out using two-sided α=0.05 level tests, unless specified otherwise.

The primary endpoint analysis will compare the MMR response rate achieved at 12 months from Day 1 treatment with first-line imatinib between dasatinib and imatinib arms using the Cochran-Mantel-Haenszel test stratified by Sokal score (high, intermediate, low, and unknown) and time from molecular analysis to randomization ($\leq$ 4 weeks vs > 4 weeks). The primary analysis will be performed on all randomized subjects. A 95% exact confidence interval (two-sided) for the difference in MMR rate at 12 months will be computed.

Subjects who are crossed over after randomization to dasatinib will be considered non-responders for any response rate analysis.

The secondary efficacy endpoints include time to MMR, time to MR[4 5], PFS, and OS. These endpoints will be tested hierarchically in the order listed.

Time to event endpoints will be estimated for each treatment group using Kaplan-Meier and Brookmeyer-Crowley methods. Time to event endpoints will be compared between the dasatinib group and imatinib group using a two-sided stratified log-rank test with Sokal score and the time between 3 month molecular assessment and randomization ($\leq$ 4 weeks vs > 4 weeks) as the stratification factors.

Response rates for the tertiary endpoints listed above at each study visit and associated Clopper-Pearson two-sided 95% confidence intervals will be estimated for each treatment group. For the response rate analyses, any subject

[redacted]

Safety: Descriptive statistics will be provided for safety data for all treated subjects.

The safety analysis will report the frequency of all adverse events and the laboratory abnormalities, as well as the frequency of interruptions, dose reductions and treatment discontinuation for toxicity. Summary tables will be presented by treatment arm.

Toxicity rates, using the worst CTC Grade per subject, for selected Grade 3 or above drug-related adverse events (e.g., fluid retention, pleural/pericardial effusion, congestive heart failure (CHF), cardiac dysfunction, rash, neutropenia, thrombocytopenia, anemia, leucopenia, AST, ALT, total bilirubin and dose reduction/interruption due to toxicity) will be compared between the two treatment arms using the Fisher exact test.

Adverse events occurring on or after Day 1 of receiving treatments and no later than 30 days following the last day of treatments will be considered on-study. In the absence of evidence of discontinuation of therapy, subjects are assumed to be still on-study.

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

[redacted]

TABLE OF CONTENTS

[redacted]

1.2 Research Hypothesis

Patients with CP-CML with BCR-ABL transcript level >10% IS after 3 months of treatment with first-line imatinib 400mg will achieve a greater rate of MMR by early switching to dasatinib therapy 100mg QD compared with continued treatment with imatinib at any dose selected by the investigator.

1.3 Objectives(s)

1.3.1 Primary Objective

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

1.3.2 Secondary Objectives

To compare the following between both treatment arms:

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

[redacted]

[redacted]

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.

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

Please see Appendix 1 for additional information regarding the BMS Informed Consent Procedures.

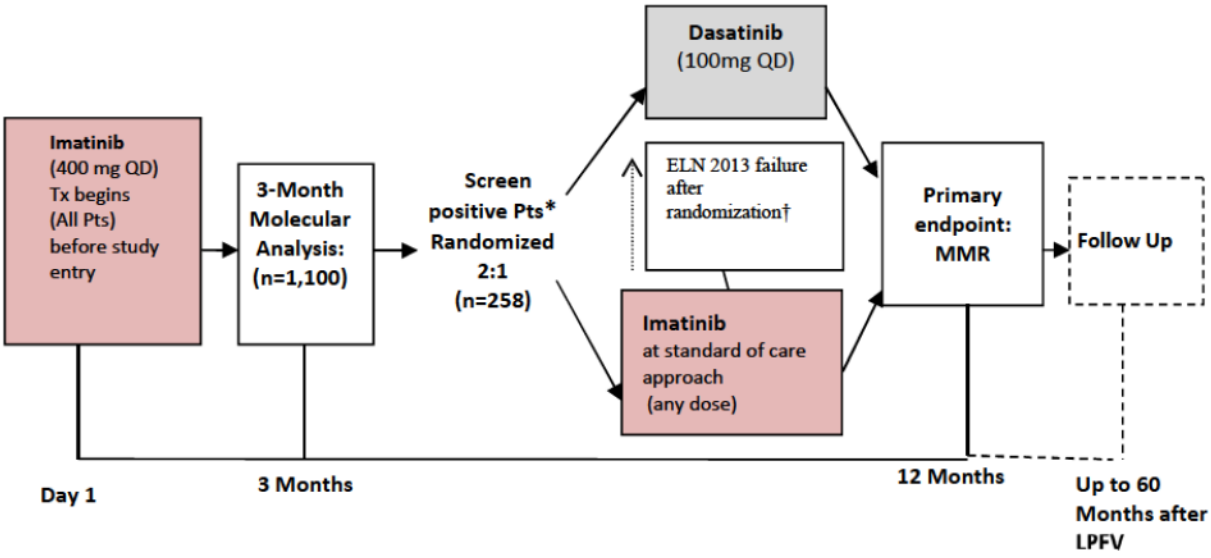
3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

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

Patients will sign the informed consent form before any screening assessment is conducted. The 3- month molecular sample, part of the screening procedure required to establish eligibility, will be analyzed in the central lab. Patients treated with imatinib preceding the 3-month molecular response assessment are considered the screened population. Screened patients with a transcript level of 10% IS or less after 3 months of imatinib 400 mg treatment are excluded from the study and will be considered screen failures. The schematic for the study design is presented in Figure 1.

Figure 1: Study Design



Screen positive patients are those who achieved CHR, but with > 10% IS BCR-ABL at 3 months. Patients with transcript levels ≤10% IS are screen failures.

† Patients randomized to imatinib, meeting ELN 2013 failure criteria [Appendix 8], and without dasatinib-resistant mutations (eg T315I/A, F317L, V299L) will be crossed over to the dasatinib arm. Crossover patients will begin study assessments specified in Table 5.1B from Day 1 of dasatinib dosing

LPFV=Last patient, first visit; MMR=major molecular response; Pts=patients; QD=once daily; Tx=treatment.

Randomization may take place up to a maximum of 8 weeks after the 3-month molecular analysis.

Randomization will be stratified by:

1. Sokal score: High, Intermediate, Low, or Unknown
2. Time between 3 month molecular assessment and randomization:
   (≤ 4 weeks vs > 4 weeks)

During the study, patients randomized to the imatinib arm who meet the ELN 2013 criteria of failure [Appendix 8] will be crossed over to the dasatinib arm, unless the patients have dasatinib-resistant mutations (eg T315I/A, F317L, V299L). For response rate analyses, these patients will be considered non-responders.

Visit schedules for crossover patients will be calculated from the date of treatment with dasatinib (Day 1) and assessments at Month 3, Month 6. Month 12, etc, specified in Table 5.1B, will be calculated from that date. Patients who cross over will be followed every 3 months for the first

24 months, and every 6 months up to 60 months, then annually according to the schedule specified in Table 5.1B.

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

For patients who continue their assigned treatment beyond 24 months, safety assessments will be conducted every 6 months up to 60 months then annually and cytogenetic assessment (conventional or FISH [peripheral blood]) every year (for durability of CCyR) as specified in the Time and Events Schedule, presented in Section 5.1.

An end of treatment visit is required for all patients. The patients who remain on the study after Month 60 will be assessed yearly and at study close. If the yearly assessment has occurred within 3 months of study close, the yearly assessment will be the end of study visit.

All subjects will be followed yearly for progression-free survival and OS. Contact with subjects who discontinue study therapy early due to disease progression, treatment failure or intolerance to study medication will be maintained annually after the end-of-treatment visit until the subject dies, the subject is lost to follow-up, or the study data collection has ended. The study will end 5 years after the last patient's first visit.

Once a subject is taken off treatment, study-related toxicities will be followed at least every 4 weeks until resolved to baseline (or CTC Grade ≤ 1), stabilized, or deemed irreversible.

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.

According to the BMS post-study drug policy, subjects who have successfully completed participation in this trial and who are medically stable on the current regimen at study completion and who do not have access to the marketed drug (or are unable to receive reimbursement through other means) may be eligible to continue to receive the medication they were originally assigned in the trial. No switches will be allowed. Only locally marketed products will be provided. The drugs provided to a subject will be limited to the marketed drugs made available in the clinical trial in which the subject was treated. If a newer formulation of marketed product is not available, an earlier formulation will be provided. Safety monitoring and evaluation will be the sole responsibility of the investigator. Prior to the termination of any subject, BMS will provide and discuss available options with the principal investigator.

BMS will no longer provide drug if any of the following occurs:

- Subject no longer benefits medically on current regimen, as determined by the investigator
- Subject is able to receive financial reimbursement through other means
- Subject expires

3.3 Study Population

Any patient beginning first line imatinib therapy fulfilling inclusion criteria (other than criterion 2a) and exclusion criteria can be considered for the study. Informed consent must be signed before any screening assessments are conducted. The 3 month molecular response assessment will be performed at the central lab as part of the study screening procedures. Screened patients with a BCR-ABL transcript level of 10% IS or less after 3 months of imatinib 400 mg treatment will be excluded from the study.

For entry (randomization) into the study, all of the following criteria MUST be met.

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Patient willing and able to give informed consent.

2. Target Population

a) CP-CML Ph+ patients with CHR but with BCR-ABL level >10% IS 3 months of imatinib 400mg treatment. (Imatinib transient dose adjustments due to AEs are allowed with a maximum of 2 weeks interruption of treatment with imatinib (cumulative) within the 3 month period before randomization). Imatinib monotherapy must have been started within 6 months of CP-CML diagnosis (Ph + /BCR-ABL detection).

b) Currently tolerating imatinib 400mg QD. Patients with prior imatinib treatment interruption or dose reductions are required to be on treatment with 400 mg imatinib for two weeks immediately prior to randomization to ensure tolerance to imatinib.

c) ECOG performance status = 0 – 2 (Appendix 2)

d) Adequate renal function defined as serum creatinine ≤3 times the institutional upper limit of normal (ULN).

e) Adequate hepatic function defined as: total bilirubin ≤2.0 times the institutional ULN; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 times the institutional ULN.

f) 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. Subjects with low K or Mg levels, total serum Ca and/or ionized Ca can be repleted to allow for protocol entry.

Rescreening is permitted in the event of temporary biochemical abnormalities.

3. Age and Reproductive Status

a) Men and women, ages ≥18 years

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 start of study drug.

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception starting at the time of enrollment for the duration of treatment with study drug (dasatinib or imatinib)/ 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 the duration of treatment with study drug (dasatinib or imatinib) 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 10.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Previous diagnosis of accelerated phase or blast crisis

b) Subjects with clonal evolution in Ph+ cells observed in ≥2 metaphases at baseline bone marrow cytogenetic test, unless the same abnormalities were present at diagnosis. Patients with no evidence of clonal evolution, including those patients whose cytogenetic testing fails or bone marrow aspiration is a dry tap at 3 months, are eligible for the study.

c) Subjects with less than CHR after 3 months of imatinib treatment or lost CHR after initial achievement

d) Documented T315I/A, F317L, or V299L mutations (if already available – not required for screening)

2. Medical History and Concurrent Diseases

a) A serious uncontrolled medical disorder or active infection that would impair the ability of the subject to receive protocol therapy

   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.

b) Uncontrolled or significant cardiovascular disease, including any of the following:

   i) Congestive cardiac failure (NYHA > Class 2) within 3 months

   ii) Diagnosed or suspected congenital long QT syndrome

   iii) Any history of significant ventricular arrhythmias; for example ventricular tachycardia (VT), ventricular fibrillation (VF), and Torsade de Points (TdP).

   iv) Prolonged QTc interval on pre-entry electrocardiogram

   v) Any history of second or third degree heart block (may be eligible if the subject currently has a pacemaker)

   vi) Unstable angina within 3 months which belongs to the spectrum of clinical presentation of Acute Coronary Syndrome (ACS)

   vii) Prior myocardial infarction within 6 months

   viii) Uncontrolled hypertension: inability to maintain blood pressure below the upper limit of 140/90 mmHg.

c) Pulmonary arterial hypertension

d) Pleural or pericardial effusions of any grade at randomization are excluded. Subjects previously diagnosed with pleural/pericardial effusion of any grade resolved at the time of randomization are allowed.

e) History of significant bleeding disorder unrelated to CML, including

   i) Diagnosed congenital bleeding disorders (eg, von Willebrand's disease)

   ii) Diagnosed acquired bleeding disorder within one year (eg, acquired anti-factor VIII antibodies)

f) Prior or concurrent malignancy, except for 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

3. Prohibited treatments and/or other treatments

a) Subject with any anti-CML other than imatinib (except HU or anagralide)

b) Subjects with prior stem cell transplantation and/or high dose chemotherapy for CML

c) Prior chemotherapy for peripheral stem cell mobilization. (Prior collection of unmobilized peripheral blood stem cells is permitted.)

d) Subjects currently taking drugs that are generally accepted to have a risk of causing Torsades de Pointes (Section 3.4.1).

4. Allergies and Adverse Drug Reaction

a) Subjects intolerant to imatinib 400mg QD prior to enrollment.

b) 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) Prisoners or subjects who are involuntarily incarcerated

b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

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

3.4.1 Prohibited and/or Restricted Treatments

No other therapy for the treatment of CML with the exception of HU or anagrelide is allowed. HU and anagrelide to treat clinically significant leukocytosis and thrombocytosis as determined by the treating physician will be permitted while the subject is on study. The use of HU or anagrelide or any colony stimulating factors must be clearly documented in the CRF.

Medications associated with QT interval prolongation that are prohibited on 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.

Refer to http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists.html for a comprehensive list of drugs which may cause QTc prolongation and Torsade De Pointes. Patients are prohibited from taking medications listed in the Known Risk of Torsade de Pointes Category.

3.4.2 Other Restrictions and Precautions

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 enrolled in this study should not begin 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 beginning 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.[30]

Additionally, strong to moderate CYP3A4 inhibitors (eg, 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 concurrently administered 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_2 antagonists. Short-acting antacid agents 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

Hydroxyurea/Anagrelide/Hematopoietic Growth Factors:

The use of hydroxyurea to keep the WBC <50,000/mm³ is permitted. Anagrelide may also be administered to control platelet counts (>1,000,000/mm³) at the investigator's discretion. No other anti-cancer agents including chemotherapy, radiation therapy and anti-cancer biologic agents are permitted during this trial. Use of G-CSF, GM-CSF, erythropoietin or darbepoetin is allowed on study.

3.5 Discontinuation of Subjects from Treatment

Subjects MUST discontinue study treatment for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- 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 (see Section 6.4)
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- In the opinion of the investigator, continued participation in the study is not in the best interest of the subject
- QTcF value >530 msec
- If pulmonary arterial hypertension is confirmed, study drug should be permanently discontinued.
- Disease progression (as defined in Section 5.4.2.1) or treatment failure despite dose escalation

Note: Patients who are in treatment failure (per ELN 2013) on imatinib therapy at any time point during the treatment will be crossed-over to the dasatinib arm unless they harbor dasatinib resistant mutations.

All subjects who discontinue study treatment 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 or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (CRF) page.

3.6 Post Treatment Study Follow up

In this study, progression and overall survival are key endpoints of the study. Post treatment study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 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 the 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

All protocol-specified investigational products are considered study drug. See Table 4.1.

4.1 Study Treatments

Table 4.1: Product Description

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Dasatinib	20 mg, 50 mg, 80 mg, 100 mg and 140 mg	Various packaging configurations Open label	Not applicable	White to off-white, biconvex, film-coated tablets	Refer to label on container or package insert/ summary of product characteristics
Imatinib	100 mg, 400 mg	Various packaging configurations Open label	Not applicable	Very dark yellow to brownish orange, 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 products are dasatinib and imatinib. BMS will provide all dasatinib associated with this protocol. Imatinib will be obtained by the site's standard prescribing procedures. If necessary, imatinib may be supplied by BMS according to country availability and specific regulatory requirements.

4.1.2 Noninvestigational 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 noninvestigational products.

In this protocol, there are no 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).

4.2 Method of Assigning Subject Identification

When the subject signs the informed consent, which must precede any screening assessment, the investigative site will make an initial phone call (using a 24 hour toll-free number) to an interactive voice response system (IVRS). As part of the screening procedure, at 3 months (1 month = 30 days) (±2 weeks) after Day 1 treatment with first-line imatinib, a blood sample for molecular analysis (Q-PCR) will be analyzed in the central lab for each subject. Those subjects with greater than 10% IS BCR-ABL at 3 months and who also meet all other screening criteria will be eligible for the study. The investigative site will then call the IVRS for the second time (using a 24-hour toll-free number) when the subject is either screen failed or is randomized to a treatment arm.

The permuted block randomization procedure will minimize the imbalance between treatment arms within each of the following stratification factors: Sokal score[31] (High, Intermediate, Low, or Unknown) and time between 3-month molecular analysis and randomization (≤4 weeks vs >4 weeks).

The study will be open for enrollment until the planned number of 258 subjects are randomized: 172 in dasatinib arm and 86 in imatinib arm.

Randomization will be stratified by:

1. Sokal score: High, Intermediate, Low, or Unknown
2. Time between 3 month molecular assessment and randomization: (≤ 4 weeks vs > 4 weeks).

Specific instructions for the central enrollment and randomization procedures will be provided to the sites in a separate procedure manual. Only authorized personnel will be granted access to the telephone system. Prior to calling the IVRS for each subject, an Enrollment Information Worksheet should be completed, and a copy of the worksheet should be at hand. It is the responsibility of the investigator to ensure that the subject is eligible for the study before enrolling/registering the subject via IVRS. The following information will be required when the phone call is placed to the central enrollment center:

At enrollment:

1) Callers User ID (identification) and PIN (personal identification number), which are assigned to each authorized investigational site staff member by the IVRS vendor
2) Subject's date of birth and gender

At randomization:

3) Sokal score (refer to below)
4) Time between 3 month molecular assessment and randomization.

The information provided by the IVRS will consist of a unique identification number (subject number) at enrollment and assigned treatment at randomization. The subject number must be used on all further documentation and correspondence, including CRFs.

The Sokal Score is calculated using the following formula, with data from the period of original diagnosis of CML and prior to the subject receiving any treatment for CML:

Score = Exp 0.0116 X (age in years – 43.4) + 0.0345 X (spleen in cm below costal margin (maximum distance) – 7.51) + 0.188 X [(platelet count / 700)^2 - 0.563] + 0.0887 X (blast cells (in percent) – 2.10)

Score	Risk Category
Score < 0.8	Low risk
0.8 – 1.2	Intermediate risk
Score > 1.2	High risk
Score Unknown:	Unknown

4.3 Selection and Timing of Dose for Each Subject

Dasatinib

Dasatinib will be administered orally at a dose of 100mg QD. Subjects may adjust the time they take dasatinib as long as they take the drug approximately every 24 hours.

Subjects will be treated with dasatinib until disease progression, treatment failure, unacceptable toxicity, the investigator and the subject feel that it is in the best interest of the subject to discontinue treatment, withdrawal of subject's consent, for reasons outlined in Section 3.5, or until a maximum of 60 months from the randomization of the last patient.

Imatinib

Imatinib will be administered orally at a dose of ≥400mg QD or BID, depending on the dose chosen. Each dose should be administered with a meal and taken with a large glass of water. Subjects may adjust the time they take imatinib as long as they take the drug every 24 hours for 400mg and 600mg dosing or every 12 hours for 400mg BID dosing and follow instructions regarding meals.

Subjects will be treated with imatinib until disease progression, treatment failure, unacceptable toxicity, the investigator and the subject feel that it is in the best interest of the subject to discontinue treatment, withdrawal of subject's consent for reasons outlined in Section 3.5, or until a maximum of 60 months from the randomization of the last patient.

4.3.1 Dose Modifications

According to the response and the toxicity, dose modifications will follow the standard of care recommendations.

Imatinib doses below 400mg are not recommended in this protocol unless considered by the investigator as in the best interest of the patient.

Dasatinib doses below 50mg are not recommended in this protocol unless considered by the investigator as in the best interest of the patient.

Dosing above 180mg QD of dasatinib or 800mg/day of imatinib is prohibited.

4.3.2 Dose Escalation Guidelines

Dose escalation for less than optimal response (according to ELN 2013 criteria [Appendix 8]) is permitted in both arms unless intolerance is encountered.

4.3.2.1 Dasatinib

For subjects dose-reduced to 80mg QD of dasatinib due to hematologic or non-hematologic toxicities as described in Section 4.3.3, the dose of dasatinib may be re-escalated to 100mg QD, if at least 1 month after the dose reduction: (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 ≥ grade 2 non-hematologic toxicities.

For subjects at 100mg QD with less than optimal response or treatment failure (according to ELN 2013 criteria [Appendix 8]), the dasatinib dose may be increased to 140mg QD provided that (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 ≥ grade 2 non-hematologic toxicities.

4.3.2.2 Imatinib

Doses greater than 600mg are not recommended in patients with mild renal impairment (CrCL = 40 - 59 mL/min). For patients with moderate renal impairment (CrCL = 20 - 39 mL/min), doses greater than 400mg are not recommended. Imatinib should be used with caution in patients with severe renal impairment.

For subjects dose-reduced to a lower dose of imatinib due to hematologic or non-hematologic toxicities as described in Section 4.3.3, the dose of imatinib may be increased to the initial dose if at least 1 month after the dose reduction: (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 ≥ Grade 2 non-hematologic toxicities.

For subjects at the randomization dose of imatinib with less than optimal response but not in the failure category (according to ELN 2013 criteria [Appendix 8]), the imatinib dose may be increased to a maximum of 800mg provided that (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 ≥ grade 2 non-hematologic toxicities

4.3.3 Dose Reduction Guidelines

The Dose Reduction Guidelines for imatinib and dasatinib are summarized in Table 4.3.3.

Dose interruptions or reductions for dasatinib- or imatinib-related adverse events (possibly, probably or certainly related) are described in Table 4.3.3. 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.

Table 4.3.3: Summary of Dose Reduction Guidelines

	Dasatinib	Imatinib
Hematologic		
Grade 1/2	No Dose Interruption/Reduction	No Dose Interruption/Reduction
Grade ≥ 3 ANC and/or platelets	Hold therapy Resume @ 100mg after recovery to ≤ Gr1 If recurrence Hold therapy Resume @ 80mg after recovery to ≤ Gr1 If recurrence @ 80 Hold therapy Re-challenge @ 80mg after recovery to ≤ Gr1 If recurrence after re-challenge Reduction to 50mg is required	Hold therapy Resume @ starting dose after recovery to ≤ Gr1 If recurrence Hold therapy Resume @ lower dose level after recovery to ≤ Gr1 If recurrence @ lower level Hold therapy Re-challenge @ the same dose after recovery to ≤ Gr1 If recurrence after re-challenge Reduction to second lower dose level is required
Non-Hematologic		
Grade 1	No Dose Interruption/Reduction	No Dose Interruption/Reduction
Grade 2	Hold therapy if deemed necessary by the investigator Resume @ 100mg after recovery to ≤ Gr1 If recurrence @ 100 Hold therapy Resume @ 80mg after recovery to ≤ Gr1 If recurrence @ 80 Reduction to 50mg is required If recurrence @ 50 Consider treatment discontinuation	Hold therapy if deemed necessary by the investigator Resume @ starting dose after recovery to ≤ Gr1 If recurrence @ starting dose Hold therapy Resume @ lower dose level after recovery to ≤ Gr1 If recurrence @ lower dose Reduction to second lower dose is required If recurrence @ second lower dose Consider treatment discontinuation
Grade ≥ 3	Hold therapy Resume @ 80mg after recovery to ≤ Gr1 If recurrence @ 80 Hold therapy Resume at 50mg after recover to ≤ Gr 1	Hold therapy Resume @ lower dose after recovery to ≤ Gr1 If recurrence @ lower dose: Hold therapy Resume @ second lower dose after recovery to ≤ Gr 1

Table 4.3.3: Summary of Dose Reduction Guidelines

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

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 Adherence

Patient adherence will be evaluated through a patient-reported questionnaire. The Morisky Medication Adherence Scale-8 items, (MMAS-8), is a validated self-reported measure of medication adherence. The scale is a commonly used adherence tool composed of yes/no questions about past medication use, and it is simple to use. Each item measures a specific medication-taking behavior. Response categories are yes/no for each item with a dichotomous response and a 5-point Likert response for the last item. Patients with higher scores are predicted to be more adherent to prescribed therapies, while patients with lower scores are at greater risk for nonadherent behavior.

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.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1A: Screening Procedural Outline (CA180399)

Procedure	Screening Visit	Visit 1 (Randomization)	Notes Randomization may occur up to 8 weeks after the screening molecular analysis.
Eligibility Assessments			**Eligibility assessments may be conducted prior to the screening molecular analysis.**
Informed Consent	X		
Inclusion/Exclusion Criteria	X		
Medical History	X		
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. For subjects randomized and treated prior to Amendment 07 (ie, incorporation of HBV serology test), a HBV serology test has to be performed once, if HBV testing was not conducted within 1 year prior to randomization. Results must be recorded on the CRF. See Section 5.3 for recommendations regarding subjects with positive HBV serology.**
Pregnancy test	X		**At screening and within 24 hours prior to initiation of therapy.**

Table 5.1A: Screening Procedural Outline (CA180399)

Procedure	Screening Visit	Visit 1 (Randomization)	Notes
			Randomization may occur up to 8 weeks after the screening molecular analysis.
Review Contraception Requirements	X	X	**Review contraception requirements presented in Section 3.3.1 and Appendix 10 with both WOCBP and male subjects.**
Mutational analysis	X		**Samples for mutational analysis will be drawn at screening, but no analysis results will be required for study participation.**
Safety Assessments			
Physical Examination, vital signs and performance status	X		
Assessment of signs and symptoms	X		
Concomitant medications	X		
Adverse Events Assessment	X		
ECG	X		**ECGs at baseline (screening), then as clinically indicated**
Echocardiogram	X		
Serum chemistry	X		**Obtained within 72 hours prior to randomization.**
Chest X-ray	X		
Efficacy-Laboratory Tests			
CBC with diff, platelets	X		**Obtained within 72 hours prior to randomization.**
Cytogenetics	X		**Conventional cytogenetic assessment required at screening to ensure absence of clonal evolution.**
Molecular analysis (Q-PCR)	X		**Screening molecular analysis by Q-PCR will be**

Table 5.1A: Screening Procedural Outline (CA180399)

Procedure	Screening Visit	Visit 1 (Randomization)	Notes
			Randomization may occur up to 8 weeks after the screening molecular analysis.
			performed 3 months (1 month = 30 days) (+/- 2 weeks) after first dose of imatinib. Q-PCR will be performed in a centralized lab.
Morisky Medication Adherence Scale		X	
Clinical Drug Supplies			
Randomize		X	Those supplied by the sponsor or sourced by the investigator
Dispense/prescribe study drugs		X	

Table 5.1B: Short-term Procedural Outline Up to 24 Months (CA180-399)

Procedure	Treatment Period			Notes
	Month 4 or 5 (± 3 days) Month 3 for crossover patients (± 3 days)	Month 6, 9, 12 (± 10 days)	Month 15, 18, 21, 24 (± 10 days)	All time-points calculated from Day 1 of first-line tx w/imatinib. Schedule Month 4 or Month 5 visit at least two weeks after randomization (start of study drug). A month 4 or 5 visit should be completed, except when the subject is randomized less than two weeks before month 5. In that instance, the next visit after randomization is at Month 6. For Cross over Patients, Day 1 is first day of tx with dasatinib. For these patients, no additional assessments are to be done on Day 1, except for an ECG and an echocardiogram, if not done in the prior 2 months. A CBC will be done 2 weeks after dasatinib start.
Safety Assessments				
Physical Examination, vital signs and performance status	X	X	X	
Assessment of signs and symptoms	X	X	X	
Adverse Events Assessment	X	X	X	
Concomitant medications	X	X	X	
ECG				ECGs at baseline (screening) and as clinically indicated. For patients who cross over to dasatinib due to imatinib failure, an ECG and echocardiogram will be performed prior to dasatinib initiation if ≥ 2 months has elapsed since the most

Table 5.1B: Short-term Procedural Outline Up to 24 Months (CA180-399)

Procedure	Treatment Period			Notes
	Month 4 or 5 (± 3 days) Month 3 for crossover patients (± 3 days)	Month 6, 9, 12 (± 10 days)	Month 15, 18, 21, 24 (± 10 days)	All time-points calculated from Day 1 of first-line tx w/imatinib. Schedule Month 4 or Month 5 visit at least two weeks after randomization (start of study drug). A month 4 or 5 visit should be completed, except when the subject is randomized less than two weeks before month 5. In that instance, the next visit after randomization is at Month 6. For Cross over Patients, Day 1 is first day of tx with dasatinib. For these patients, no additional assessments are to be done on Day 1, except for an ECG and an echocardiogram, if not done in the prior 2 months. A CBC will be done 2 weeks after dasatinib start.
				recent ECG and echocardiogram.
Pregnancy Test	Monthly	Monthly	Monthly	For WOCPB, a pregnancy test must be performed monthly. When a monthly study visit is not required, a home pregnancy test must be performed, and the results entered on the Pregnancy Testing Log (Appendix 9). The log must be brought to every study visit.
Review Contraception Requirements	At every study visit	At every study visit	At every Study visit	Review contraception requirements presented in Section 3.3.1 and Appendix 10 with both WOCBP and male subjects
Echocardiogram				At baseline (screening), and as clinically indicated. For patients crossed over to dasatinib

Table 5.1B: Short-term Procedural Outline Up to 24 Months (CA180-399)

Procedure	Treatment Period			Notes
	Month 4 or 5 (± 3 days) Month 3 for crossover patients (± 3 days)	Month 6, 9, 12 (± 10 days)	Month 15, 18, 21, 24 (± 10 days)	All time-points calculated from Day 1 of first-line tx w/imatinib. Schedule Month 4 or Month 5 visit at least two weeks after randomization (start of study drug). A month 4 or 5 visit should be completed, except when the subject is randomized less than two weeks before month 5. In that instance, the next visit after randomization is at Month 6. For Cross over Patients, Day 1 is first day of tx with dasatinib. For these patients, no additional assessments are to be done on Day 1, except for an ECG and an echocardiogram, if not done in the prior 2 months. A CBC will be done 2 weeks after dasatinib start.
				due to imatinib failure, an ECG and echocardiogram will be performed prior to dasatinib initiation if ≥ 2 months has elapsed since the most recent ECG and echocardiogram.
Chest X-Ray				CXR at baseline (screening) and as clinically indicated.
Serum chemistry	X	X	X	

Table 5.1B: Short-term Procedural Outline Up to 24 Months (CA180-399)

Procedure	Treatment Period			Notes
	Month 4 or 5 (± 3 days) Month 3 for crossover patients (± 3 days)	Month 6, 9, 12 (± 10 days)	Month 15, 18, 21, 24 (± 10 days)	All time-points calculated from Day 1 of first-line tx w/imatinib. Schedule Month 4 or Month 5 visit at least two weeks after randomization (start of study drug). A month 4 or 5 visit should be completed, except when the subject is randomized less than two weeks before month 5. In that instance, the next visit after randomization is at Month 6. For Cross over Patients, Day 1 is first day of tx with dasatinib. For these patients, no additional assessments are to be done on Day 1, except for an ECG and an echocardiogram, if not done in the prior 2 months. A CBC will be done 2 weeks after dasatinib start.
Efficacy Assessments				
CBC with diff, platelets	X	X	X	Required at baseline (Screening), at month 4 or 5 or 6 (ie, the visit that is closest to one month after randomization), then every 3 months until month 24. After 24 months, CBC is required every 6 months or as clinically indicated. For patients randomized (or crossing over) to dasatinib, a CBC at 2 weeks is required (Additional office visit is not required: CBC results can be faxed to investigators from local lab and assessed according to dasatinib labeling recommendations.)

Table 5.1B: Short-term Procedural Outline Up to 24 Months (CA180-399)

Procedure	Treatment Period			Notes
	Month 4 or 5 (± 3 days) Month 3 for crossover patients (± 3 days)	Month 6, 9, 12 (± 10 days)	Month 15, 18, 21, 24 (± 10 days)	All time-points calculated from Day 1 of first-line tx w/imatinib. Schedule Month 4 or Month 5 visit at least two weeks after randomization (start of study drug). A month 4 or 5 visit should be completed, except when the subject is randomized less than two weeks before month 5. In that instance, the next visit after randomization is at Month 6. For Cross over Patients, Day 1 is first day of tx with dasatinib. For these patients, no additional assessments are to be done on Day 1, except for an ECG and an echocardiogram, if not done in the prior 2 months. A CBC will be done 2 weeks after dasatinib start.
Cytogenetics (conventional or FISH[peripheral blood])		Months 6 and 12	Every 6 months until CCyR, then annually	Conventional cytogenetics are recommended until CCyR is achieved and confirmed. PB-FISH is allowed as a substitute for conventional assessment, especially after CCyR is achieved, to confirm the durability of response.
Molecular analysis/Q-PCR	X	X	X	Q-PCR labs will be performed in a centralized lab and expressed on an international scale at baseline (screening), month 4, 5, or 6 and every 3 months thereafter up to month 24.
Mutational analysis	X	X	X	Samples for mutational analysis will be drawn at screening and every 3 months through month 24, every 6 months

Table 5.1B: Short-term Procedural Outline Up to 24 Months (CA180-399)

Procedure	Treatment Period			Notes
	Month 4 or 5 (± 3 days) Month 3 for crossover patients (± 3 days)	Month 6, 9, 12 (± 10 days)	Month 15, 18, 21, 24 (± 10 days)	All time-points calculated from Day 1 of first-line tx w/imatinib. Schedule Month 4 or Month 5 visit at least two weeks after randomization (start of study drug). A month 4 or 5 visit should be completed, except when the subject is randomized less than two weeks before month 5. In that instance, the next visit after randomization is at Month 6. For Cross over Patients, Day 1 is first day of tx with dasatinib. For these patients, no additional assessments are to be done on Day 1, except for an ECG and an echocardiogram, if not done in the prior 2 months. A CBC will be done 2 weeks after dasatinib start.
				from month 24 until the end of study, and then stored. Samples can also be drawn at an unscheduled visit if the clinical status triggers an unscheduled visit. Mutational analysis will be performed on stored samples, at time of any suboptimal response, treatment failure, progression, at the end of treatment or prior to any change in therapy.
Morisky Medication Adherence Scale (MMAS-8)	X	Months 6 and 12	Months 18 and 24 only	
Clinical Drug Supplies				
Dispense/prescribe study drug	X	X	X	
Assess Study Medication Usage	X	X	X	

Table 5.1C: Procedural Outline Months 30 - Study Close/End of Treatment (CA180-399)

Procedure	Treatment Period		End of Treatment[b] or at the study close (60 months after LPFV)	Notes
	Months 30, 36, 42, 48, 54, 60	Month 72[a] and yearly until the study close		All time-points calculated from Day 1 of first-line tx w/imatinib or from Day 1 of tx w/dasatinib for cross-over patients. All visits are ± 10 days The study will continue up to 60 months after the last patient, first visit. End of treatment visit is required for all patients.
Safety Assessments				
Physical Examination, vital signs and performance status	X	X	X	
Assessment of signs and symptoms	X	X	X	
Adverse Events Assessment	X	X	X	See Section 6 for adverse event reporting including reporting requirements for Serious Adverse Event
Concomitant medications	X	X	X	
ECG				As clinically indicated. For patients crossing over to dasatinib due to imatinib failure, an ECG and echocardiogram will be performed prior to dasatinib initiation if ≥ 2 months have elapsed since the most recent ECG and echocardiogram.

Table 5.1C: Procedural Outline Months 30 - Study Close/End of Treatment (CA180-399)

Procedure	Treatment Period		End of Treatment[b] or at the study close (60 months after LPFV)	Notes
	Months 30, 36, 42, 48, 54, 60	Month 72[a] and yearly until the study close		All time-points calculated from Day 1 of first-line tx w/imatinib or from Day 1 of tx w/dasatinib for cross-over patients. All visits are ± 10 days The study will continue up to 60 months after the last patient, first visit. End of treatment visit is required for all patients.
Pregnancy Test	Monthly	Monthly	X	For WOCPB, a pregnancy test must be performed monthly. When a monthly study visit is not required, a home pregnancy test must be performed, and the results entered on the Pregnancy Testing Log (Appendix 9). The log must be brought to every study visit.
Review Contraception Requirements	At every study visit	At every study visit	X	Review contraception requirements presented in Section 3.3.1 and Appendix 10 with both WOCBP and male subjects
Echocardiogram				As clinically indicated. For patients who cross over to dasatinib due to imatinib failure, an ECG and echocardiogram will be performed prior to dasatinib initiation if ≥ 2 months have elapsed since the most recent ECG and echocardiogram.
Chest X-Ray				As clinically indicated
Serum chemistry	X	X	X	

Table 5.1C: Procedural Outline Months 30 - Study Close/End of Treatment (CA180-399)

Procedure	Treatment Period		End of Treatment[b] or at the study close (60 months after LPFV)	Notes
	Months 30, 36, 42, 48, 54, 60	Month 72[a] and yearly until the study close		All time-points calculated from Day 1 of first-line tx w/imatinib or from Day 1 of tx w/dasatinib for cross-over patients. All visits are ± 10 days The study will continue up to 60 months after the last patient, first visit. End of treatment visit is required for all patients.
Efficacy Assessments				
CBC w diff, platelets	X	X	X	
Cytogenetics (Conventional or FISH [peripheral blood])	X	X	X	Conventional cytogenetics are recommended until CCyR is achieved and confirmed. FISH-PB is allowed as a substitute for conventional assessment, especially after CCyR is achieved, to confirm the durability of response.
Molecular analysis/Q-PCR	X	X	X	Q-PCR labs will be performed in a centralized lab and expressed on an international scale. For patients not in MMR at month 24, molecular analysis by Q-PCR will continue to be performed every 3 months until MMR is achieved.
Mutational analysis	X	X	X	Samples for mutational analysis will be drawn at screening and every 3 months through month 24, every 6 months from month 24 until the end of study, and then stored. Samples can also be drawn at an

Table 5.1C: Procedural Outline Months 30 - Study Close/End of Treatment (CA180-399)

Procedure	Treatment Period: Months 30, 36, 42, 48, 54, 60	Treatment Period: Month 72[a] and yearly until the study close	End of Treatment[b] or at the study close (60 months after LPFV)	Notes
				All time-points calculated from Day 1 of first-line tx w/imatinib or from Day 1 of tx w/dasatinib for cross-over patients. All visits are ± 10 days The study will continue up to 60 months after the last patient, first visit. End of treatment visit is required for all patients.
				unscheduled visit if the clinical status triggers an unscheduled visit. Mutational analysis will be performed on stored samples, at time of any suboptimal response, treatment failure, progression, at the end of treatment or prior to any change in therapy.
Dispense/prescribe Study Drug	X	X		
Morisky Medication Adherence Scale (MMAS-8)	X	X	X	

a Patients who remain on the study after Month 60 will be assessed yearly and at study close (60 months after LPFV). If the yearly assessment has occurred within 3 months prior to the study close, an end of study visit is not required.

b Survival Follow-up: In addition to the End-of-Treatment visit, which is to be conducted at the time of discontinuation of study drug for any reason or at the end of study close, contact with subjects for survival follow-up (including those subjects who discontinue before the end of the study) will be maintained annually (±14 days) after the End-of-Treatment visit to collect progression and overall survival information, until the subject dies, the subject is lost to follow-up, or study data collection has ended.

NOTE: Subjects crossed over from imatinib arm to dasatinib (per Section 3.1) must complete all study assessments until discontinuation or progression as defined in Section 5.4.2.1. When the patient crosses over, s/he starts a second line treatment and the visit schedule must start at Day 1 defined as the day of first dose of dasatinib. Assessment at M3, M6, M12, etc. must be calculated from the Day 1 date.

5.2 Study Materials

Special 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.

5.3 Safety Assessments

Signs and symptoms present within 2 weeks of starting therapy (regardless of relationship to current disease) will be obtained at baseline (screening). Study drug toxicities will be assessed continuously. Adverse events will be evaluated according to the NCI CTCAE Version 4.0.

A physical examination (including assessment of spleen and liver size), weight, performance status and vital signs, and concomitant medications, will be conducted at screening, during the treatment period at Months 4 or 5, and 6, and then every 3 months until Month 24. From Month 24 to Month 60, safety assessments will be obtained every 6 months, and after Month 60, safety assessments will be done annually, until disease progression or discontinuation of study therapy and at the end-of-treatment visit.

Chest X-Rays will be performed at baseline (screening), and as clinically indicated throughout the study.

A 12-Lead ECG to determine baseline QTc will be done at baseline (screening), and 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).

An echocardiogram will be performed at baseline (screening) and as clinically indicated.

For patients who cross over to dasatinib due to imatinib failure, an ECG and echocardiogram will be performed prior to dasatinib initiation if ≥ 2 months has elapsed since the most recent ECG and echocardiogram. When the patient crosses over, s/he starts a second line treatment and the visit schedule must start at Day 1. Visit schedules for crossover patients will be calculated from the date of treatment with dasatinib (Day 1) and assessments at Month 3, Month 6. Month 12, etc, specified in Table 5.1B, will be calculated from that date. Patients who cross over will be followed every 3 months for the first 24 months, and every 6 months up to 60 months and then annually, according to the schedule specified in Table 5.1B.

Once a subject is taken off treatment, study-related toxicities will be followed at least every 4 weeks until resolved to baseline (or CTC Grade ≤ 1), stabilized, or deemed irreversible.

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

5.3.1.1 Definition of Intolerance

Intolerance of treatment is defined as recurrent ≥Grade 3 hematologic toxicity or ≥Grade 2 non-hematologic toxicity despite dose reduction necessitating discontinuation of protocol therapy. Adverse events and other symptoms will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

5.3.1.2 Safety/Toxicity

Toxic effects will be assessed continuously. Safety and tolerability for both treatment groups will be reported for all treated subjects. Adverse events and other symptoms will be graded according to the NCI CTCAE version 4.0. Number of dose interruptions, dose reductions and treatment discontinuations for drug-related toxicity will be analyzed.

5.4 Efficacy Assessments

For the assessment of efficacy, CBC with differential and PLT count, cytogenetics and molecular analysis/Q-PCR will be conducted at baseline (screening). During the treatment period, hematology and molecular analysis/QPCR will be conducted at Months 4 or 5, Month 6 and then every 3 months until Month 24, and every 6 months up to 60 months, then annually until the end of the study. For patients not in MMR at Month 24, molecular analysis by Q-PCR will continue to be performed every 3 months until MMR is achieved.

For patients who cross over to dasatinib a CBC with differential will be done at 2 weeks, hematology and molecular analysis/QPCR will be conducted at Month 3 from the date of crossover, and then every 3 months until Month 24, and every 6 months thereafter until the end of the study.

Cytogenetics (conventional or FISH-PB peripheral blood) will be conducted at Month 6 and 12, every 6 months until CCyR and then annually. Conventional cytogenetics are recommended until CCyR is achieved and confirmed. FISH-PB peripheral blood is allowed as a substitute for conventional assessment, especially after CCyR is achieved, to confirm the durability of response. Samples for mutational analysis will be drawn at screening and every 3 months through month 24, every 6 months from month 24 up to 60 months, then annually until the end of the study, and then stored. Mutational analysis will be performed on stored samples, at time of any suboptimal response, treatment failure, progression, at the end of treatment or prior to any change in therapy. Samples for mutational analysis can also be drawn at an unscheduled visit if the clinical status triggers an unscheduled visit.

5.4.1 Efficacy Endpoints

Efficacy endpoints will be based on hematologic, cytogenetic and molecular disease assessments at predefined intervals as specified in Table 5.1A, Table 5.1B and Table 5.1C.

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+ cells in metaphase from BM sample.

The criteria for evaluation of CyR are as follows:

Complete Cytogenetic Response (CCyR): 0% Ph+ cells in metaphase in BM

Partial Cytogenetic Response (PCyR): 1 to 35% Ph+ cells in metaphase in BM

Minor Cytogenetic Response: 36 to 65% Ph+ cells in metaphase in BM

Minimal Cytogenetic Response: 66 to 95% Ph+ cells in metaphase in BM

No Cytogenetic Response: 96 to 100% Ph+ cells in metaphase in BM

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

5.4.1.3 Definition of Molecular Response

Molecular response will be assessed using BCR-ABL transcript levels measurement by RQ-PCR.

An MMR is defined according to the recommendations of Hughes et al.[5] The standardized baseline, as established in the IRIS trial, is taken to represent 100% on the international scale, and a 3-log reduction in BCR-ABL transcripts from the standardized baseline (MMR) is fixed at 0.1%. The ratio BCR-ABL/ABL or BCR is independent of the used control-gene. In this study, ABL or other housekeeping gene, will be used as the control-gene.

An MR[4,5] will be defined as a 4.5-log reduction in BCR-ABL transcript from the standardized baseline (0.0032% IS, either detectable disease $\leq$0.0032% BRC-ABL (IS) or undetectable

disease in cDNA (in same volume used for BCR-ABL) with ≥32,000 ABL transcripts. An MR^4 will be defined as a 4-log reduction in BCR-ABL transcript from the standardized baseline (either detectable disease ≤0.01% BCR-ABL (IS) or undetectable disease in cDNA (in same volume used for BCR-ABL) with ≥10,000 ABL transcripts.

The rate of MMR at 12 months is defined as the proportion of subjects who achieved an MMR at 12 months (primary endpoint) after Day 1 initiation of first-line treatment with imatinib, in patients randomized at month 3 to treatment with dasatinib 100mg QD or imatinib at any dose. Further assessments of MMR and other levels of molecular response rates will occur at various timepoints (refer to study assessments).

5.4.1.4 Time to Molecular Response

A subject's time to MMR is defined as the time from the randomization date until measurement criteria are first met for MMR.

5.4.2 Definition of Progression

5.4.2.1 Progression on Study Therapy

Any of the following events occurring while a subject is continuously on study therapy would define progression. Subjects should be on the maximum tolerated dose (as determined by the investigator) before criteria for progression are considered.

- Criteria for accelerated or blast crisis CML are met at any time (Refer to Appendix 7 for criteria).
- Death from any cause during treatment.

The date of progression will be defined as the date when any of the above criteria is first met. Subjects meeting any criterion for progression will be removed from protocol therapy.

Note: Loss of a previously achieved hematologic or cytogenetic response is considered a treatment failure, not disease progression.

5.4.2.2 Failure to First-line Treatment

Treatment failure to first-line therapy is defined as:

1. Any of the disease progression parameters above
2. At 3 months: less than complete hematologic response (These subjects will not be eligible for randomization) and/or No CyR (Ph+ >95%)
3. At 6 months: BCR-ABL >10% and/or Less than PCyR (Ph+ >35%)
4. At 12 months: BCR-ABL >1% and/or Less than CCyR (Ph+ >0%)
5. At any time during treatment, loss of CHR or CCyR; Confirmed loss of MMR (In two consecutive tests, of which one with a BCR-ABL1 transcripts level ≥ 1%), BCR-ABL1 kinase domain mutations poorly sensitive to imatinib; newly emerging CCA/Ph+

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

5.4.2.3 Overall Survival

Overall survival (OS) is defined as the time between randomization date and death date.

5.5 Pharmacokinetic Assessments

Not applicable.

5.6 Biomarker Assessments

Not applicable.

5.7 Outcomes Research Assessments

Treatment adherence will be assessed through a patient-reported questionnaire (i.e., MMAS).

The Morisky Medication Adherence Scale-8 items, (MMAS-8), is a validated self-reported measure of medication adherence. The scale is a commonly used adherence tool composed of yes/no questions about past medication use that is simple to use. Each item measures a specific medication-taking behavior. Response categories are yes/no for each item with a dichotomous response and a 5-point Likert response for the last item. Patients with higher scores are predicted to be more adherent to prescribed therapies, while patients with lower scores are at greater risk for nonadherent behavior.

5.8 Other Assessments

5.8.1 Laboratory 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 or FISH [peripheral blood] will be performed to monitor the subject's CyR.

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.

5.8.1.1 Hematology

CBC, differential and PLT will be obtained within 72 hours prior to randomization, at Months 4 or 5, or 6 (one month after randomization) and then every 3 months until Month 24. Following Month 24, hematology tests will be obtained every 6 months up to 60 months, then annually until disease progression or end of study therapy and at the end-of-treatment visit.

For patients randomized (or crossing over) to dasatinib a CBC at 2 weeks of dasatinib initiation is required (Additional office visit not required: CBC results can be faxed to investigators from local lab and assessed according to dasatinib labeling recommendations.)

For patients who cross over to dasatinib, CBC, differential and PLT will be obtained at Month 3 from the date of the first treatment with dasatinib, and then every 3 months until Month 24, and every 6 months up to 60 months, then annually until the end of the study.

5.8.1.2 Bone Marrow

BM aspirates will be obtained prior to randomization, then at months 6 and 12.

BM aspirates obtained 3 weeks prior to the 3-month molecular analysis time point and until randomization are acceptable for this study even if the BM aspirate was obtained before the informed consent signature.

After the first 12 months of treatment, a BM aspirate will be obtained every 6 months until CCyR is achieved and confirmed, then every 12 months thereafter.

Conventional cytogenetics is recommended until CCyR is achieved and confirmed. FISH (peripheral blood) is allowed as a substitute for conventional assessment (at all time points except screening), especially after CCyR is achieved, to confirm the durability of response.

5.8.1.3 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 at pre-treatment (within 72 hours prior to randomization) at Month 4 or 5, 6 and then every 3 months until Month 24. Following month 24, serum chemistry tests will be obtained every 6 months up to 60 months, then annually until disease progression or end of study therapy and at the end-of-treatment visit.

For patients who cross over to dasatinib, BUN, creatinine, ALT, AST, alkaline phosphatase, total bilirubin, LDH, Na, K, Mg, P, total serum or ionized Ca and uric acid will be obtained at Month 3 from the first day of treatment with dasatinib, and then every 3 months until Month 24, and every 6 months thereafter until the end of the study.

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

5.8.1.4 Pregnancy Test

For women of child-bearing potential, a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of βHCG) will be performed at screening, within 24 hours prior to start of study therapy, monthly, and 30 days after the last dose of study drug.

When a monthly study visit is not required, WOCBP will be required to use a home pregnancy test and to record the test date and results on the Pregnancy Test Log (Appendix 9). The Pregnancy test log must be brought to every study visit; log entries will be recorded in the CRF.

5.9 Results of Central Assessments

Molecular assessment will be performed in a central laboratory, and results will be communicated to the investigator site on a regular basis (eg, within 2-3 weeks). Screening molecular assessment will condition the eligibility for randomization. Subsequent molecular results may lead to treatment dosing modification.

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 casual 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 S***erious 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, [redacted] always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

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 initiation of study drug after randomization and continue up to 30 days post last dose of study drug.

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 6.1.1for 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 are treating 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 will regularly assess study progress at defined intervals (at least 3 times a year and ad-hoc as necessary), review safety data by arm including all SAEs, grade 3 and 4 AEs and discontinuations and examine critical efficacy endpoints (eg, MMR, time to MMR, PFS) of the study.

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

8 STATISTICAL CONSIDERATIONS

[redacted]

8.2 Populations for Analyses

The following data sets will be used in this study.

- **Enrolled subjects**: All subjects who signed an informed consent
- **Randomized subjects**: All subjects who are randomized
- **Treated subjects**: All subjects who are randomized and receive at least one dose of study treatment

All enrolled subjects will be used in the tabulation of subject disposition. All randomized subjects will be used in the analysis of demographics, baseline characteristics and efficacy. Safety and extent of exposure will be analyzed based on all treated subjects.

All analyses will be performed by treatment arm as randomized, except the analyses for dosing and safety, which will be analyzed by treatment arm as treated.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary endpoint for this study is the proportion of randomized subjects who achieve MMR at 12 months after the first day (Day 1) treatment with first-line imatinib in patients in each treatment group.

8.3.2 Secondary Endpoint(s)

The secondary efficacy measures comparing randomized treatment arms will be tested in the following order (see Section 8.4.2):

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

[redacted]

8.3.4 Endpoint Definitions

Efficacy

The primary efficacy endpoint, MMR at 12 months is the proportion of randomized subjects who achieve MMR at 12 months from Day 1 treatment with first-line imatinib (up to 9 months after their randomization date).

The secondary endpoints include the following:

Time to MMR (or $MR^{4.5}$) is the time between randomization date and first date that MMR (or $MR^{4.5}$) criteria are satisfied. Subjects who do not achieve MMR (or $MR^{4.5}$) will be censored according to rules that will be detailed in the statistical analysis plan (SAP).

Overall Survival (OS) is the time from randomization date to death date. Subjects who have not died will be censored on the last date they are known to be alive. Additional details and rules will be specified in the SAP.

Progression-Free Survival (PFS) is the time from randomization date to progression date or death date, whichever occurs first. Subjects who neither progress nor die will be censored. Additional details and rules will be specified in the SAP.

[redacted]

Safety

Intolerance of treatment, defined as recurrent ≥Grade 3 hematologic toxicity or ≥Grade 2 non-hematologic toxicity despite dose reduction necessitating discontinuation of protocol therapy. Adverse events and other symptoms will be assessed continuously and reported for all treated subjects, and will be graded according to the NCI CTCAE Version 4.0. Other safety endpoints include laboratory abnormalities, ECG abnormalities, as well as the frequency of interruptions, dose reductions and treatment discontinuation for toxicity.

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Descriptive statistics will be provided for demographic data and baseline (screening) patient characteristics data for all randomized subjects by and across strata.

8.4.2 Efficacy Analyses

All efficacy analyses will be performed on the population of 'all randomized subjects', and all comparisons between treatment arms will be carried out using two-sided α=0.05 level tests, unless specified otherwise.

Primary endpoint

The primary endpoint analysis will compare the MMR response rate achieved at 12 months from Day 1 treatment with first-line imatinib between the dasatinib and imatinib arms using the Cochran-Mantel-Haenszel test stratified by Sokal score (High, Intermediate, Low, and Unknown) and time from molecular analysis to randomization (≤4 weeks vs >4 weeks). The primary analysis will be performed on all randomized subjects. A 95% exact confidence interval (two-sided) for the difference in MMR rate at 12 months will be computed.

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

Secondary endpoints

The secondary efficacy endpoints include time to MMR, time to $MR^{4.5}$ PFS, and OS.

Time to event endpoints will be estimated for each treatment group using Kaplan-Meier and Brookmeyer-Crowley methods. Time to event endpoints will be compared between the dasatinib group and imatinib group using a two-sided stratified log-rank test with Sokal score and the time between 3 month molecular assessment and randomization (≤4 weeks vs >4 weeks) as the stratification factors. In addition, competing risk methodology will be taken into account for patients who die or receive a bone marrow transplant.

A sensitivity analysis of PFS and OS will be performed on the randomized subjects where subjects who are crossed over to dasatinib after treatment failure on imatinib will be censored at the date of crossover.

The secondary endpoints will only be considered for comparison between the two treatment groups if the primary endpoint is significant. The secondary endpoints are ranked as follows:

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

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

[redacted]

[redacted]

8.4.3 Safety Analyses

Descriptive statistics will be provided for safety data for all treated subjects

The safety analysis will report the frequency of all adverse events and laboratory abnormalities, as well as the frequency of interruptions, dose reductions and treatment discontinuation for toxicity. Summary tables will be presented by treatment arm.

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

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

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

8.4.4 Pharmacokinetic Analyses

Not applicable.

8.4.5 Biomarker Analysis

Not applicable.

[redacted]

8.5 Interim Analyses

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

An interim analysis is planned when all 258 subjects have been followed until month 12 (calculated from day 1 of initiation of first line imatinib. i.e., at the time of the primary endpoint final analysis). This analysis will assess the secondary efficacy endpoints time to MMR and $MR^{4.5}$ as well as safety endpoints. To account for an interim look at these 2 efficacy endpoints, an alpha level of 0.0001 will be used and the hierarchical testing described in this statistical analysis plan will be used.

This analysis will be repeated every year until the final analysis is conducted when all subjects have been followed until year 5. As a result the final analysis will be conducted using an alpha level of 0.0496 for MMR and $MR^{4.5}$.

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 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.

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 or designee 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 or the site) 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
- non-study disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retained 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 or designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

For protocol-defined IMP sourced by the site (not supplied by BMS), the site will record the lot number, if possible, and if lot number is not available, will instead record the prescription provider and prescription number.

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.

For sites using the ICON 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)

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
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
cCHR	Confirmed Complete Hematological Response
CCyR	Complete Cytogenetic Response
CyR	Cytogenetic Response
CHR	Complete Hematologic Response
CI	Confidence Interval
CML	Chronic Myeloid Leukemia
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
eg	exempli gratia (for example)
ESR	Expedited Safety Report
FSH	Follicle Stimulating Hormone
FISH	Fluorescent-In Situ Hybridization
GCP	Good Clinical Practice
GI	Gastro-Intestinal
HCG	Human Chorionic Gonadotropin
HRT	Hormone Replacement Therapy
HU	Hydroxyurea

Term	Definition
ICH	International Conference on Harmonization
IDMC	Internal Data Monitoring Committee
i.e.	id est (that is)
IEC	Independent Ethics Committee
IM	Imatinib mesylate
α-IFN	Interferon-α
INR	International Normalized Ratio
IRB	Institutional Review Board
IS	International Standard
IU	International Unit
IV	Intra Venous
IVRS	Interactive Voice Response System
K	Kalium (Potassium)
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
M	Month
MCyR	Major cytogenetic response
mg	Milligram
Mg	Magnesium
µM	microMolar
MMR	Major Molecular Response
MR	Molecular response
$MR^{4.5}$	4.5- log reduction in BCR-ABL transcript from the standardized baseline (0.0032% IS).
MR^{4}	4-log reduction in BCR-ABL transcript from the standardized baseline (0.01% IS).
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
PFS	Progression-free Survival
pH	$-\log_{10}$ hydrogen ion concentration
Ph+	Philadelphia chromosome positive

Term	Definition
PLT	Platelets
p.o.	Per os (by mouth)
PS	Performance Status
PTK	Protein Tyrosine Kinase
q	Every
QD	once daily
QPCR	Quantitative polymerase chain reaction
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)
RQ-PCR	Real-time quantitative polymerase chain reaction
SAE	Serious Adverse Event
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 ADDITIONAL ETHICAL CONSIDERATIONS

1 INFORMED CONSENT PROCEDURES

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. If the investigator makes changes to the informed consent form sample, BMS will ensure all required elements and local regulatory and legal requirements are met.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records. Prior to the beginning of the study, the investigator must have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects.

The investigator must provide the subject, or, in those situations where consent cannot be given by subjects, their legally acceptable representative with a copy of the consent form and written information about the study in the language in which the subject is most proficient. The language must be non-technical and easily understood. The investigator should allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study, then informed consent must be signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion. The subject or legally acceptable representative should receive a copy of the signed informed consent and any other written information provided to study subjects prior to subject's participation in the study.

1.1 Subjects Unable to Give Written Informed Consent

1.1.1 Minors

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the informed consent form approved for the study prior to clinical study participation. (In the event that the parents or legal guardians are unable to read, then an impartial witness should be present during the entire informed consent discussion). Whenever feasible, minors who are judged to be of an age of reason must also give their written assent by signing and dating the completed informed consent. All local laws, rules and regulations regarding informed consent of minors must be followed.

1.1.2 Subjects Experiencing Acute Events or Emergencies

A legally acceptable representative or legal guardian must provide informed consent when consent of the subject is not possible prior to clinical study participation, eg, for subjects experiencing an acute medical event such as myocardial infarction or stroke. Informed consent of the subject must additionally be obtained if they become capable of making and communicating their informed consent during the clinical study. All local laws, rules and regulations regarding informed consent of adult subjects incapable of giving informed consent must be followed.

1.1.3 Mentally Impaired or Incapacitated Subjects

Investigators (or whoever required by local regulations) should determine whether or not a mentally impaired or incapacitated subject is capable of giving informed consent and should sign a statement to that effect. If the subject is deemed mentally competent to give informed consent, the investigator should follow standard procedures. If the subject is deemed not to be mentally competent to give informed consent, a fully informed legal guardian or legally acceptable representative can be asked to give consent for, or on behalf of, the subject. All local laws, rules and regulations regarding informed consent of mentally impaired or incapacitated subjects must be followed.

Patients who are involuntarily hospitalized because of mental illness must not be enrolled in clinical studies

1.1.4 Other Circumstances

Subjects who are imprisoned or involuntarily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness must not be enrolled in clinical studies.

In circumstances where a subject's only access to treatment is through enrollment in a clinical study, eg, for subjects in developing countries with limited resources or for subjects with no marketed treatment options, the investigator must take special care to explain the potential risks and benefits associated with the study and ensure that the subject is giving informed consent.

When a subject may be in a dependent relationship with the investigator, a well-informed physician who is not engaged in the clinical study and is completely independent of the relationship between the subject and investigator should obtain the subject's informed consent.

1.1.5 Illiterate Subjects

If the subject, or, in those situations where consent cannot be given by the subject, their legally acceptable representative is unable to read, a reliable and independent witness should be present during the entire informed consent discussion. The choice of the witness must not breach the subject's rights to confidentiality. A reliable independent witness is defined as one not affiliated with the institution or engaged in the investigation. A family member or acquaintance is an appropriate independent witness. After the subject or legally acceptable representative orally consents and has signed, if capable, the witness should sign and personally date the consent form attesting that the information is accurate and that the subject, or, in those situations where consent cannot be given by subjects, their legally acceptable representative has fully understood the content of the informed consent agreement and is giving true informed consent.

1.2 Update of Informed Consent

The informed consent and any other information provided to subjects, or, in those situations where consent cannot be given by subjects, the subject's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the subject's consent, and should receive IRB/IEC approval/favorable opinion prior to use. The investigator, or a person designated by the investigator should fully inform the subject or the subject's legally acceptable representative 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.

During a subject's participation in the study, any updates to the consent form and any updates to the written information will be provided to the subject.

Protocol Number: CA1890399
IND Number: 66,971
EUDRACT Number 2011-006181-41
Date: 10 AUG 2012

Protocol CA1890399: AN OPEN LABEL, RANDOMIZED (2:1) PHASE 2B STUDY OF DASATINIB VS. IMATINIB IN PATIENTS WITH CHRONIC-PHASE CHRONIC MYELOID LEUKEMIA WHO HAVE NOT ACHIEVED AN OPTIMAL RESPONSE TO 3 MONTHS OF THERAPY WITH 400 MG IMATINIB

Amendment Number 01
Site Number: All

Study Director and Central Medical Monitor
Hesham Mohamed MD
[redacted]

This protocol amendment contains information that is confidential and proprietary to Bristol-Myers Squibb (BMS).

This amendment must be maintained with the referenced protocol.

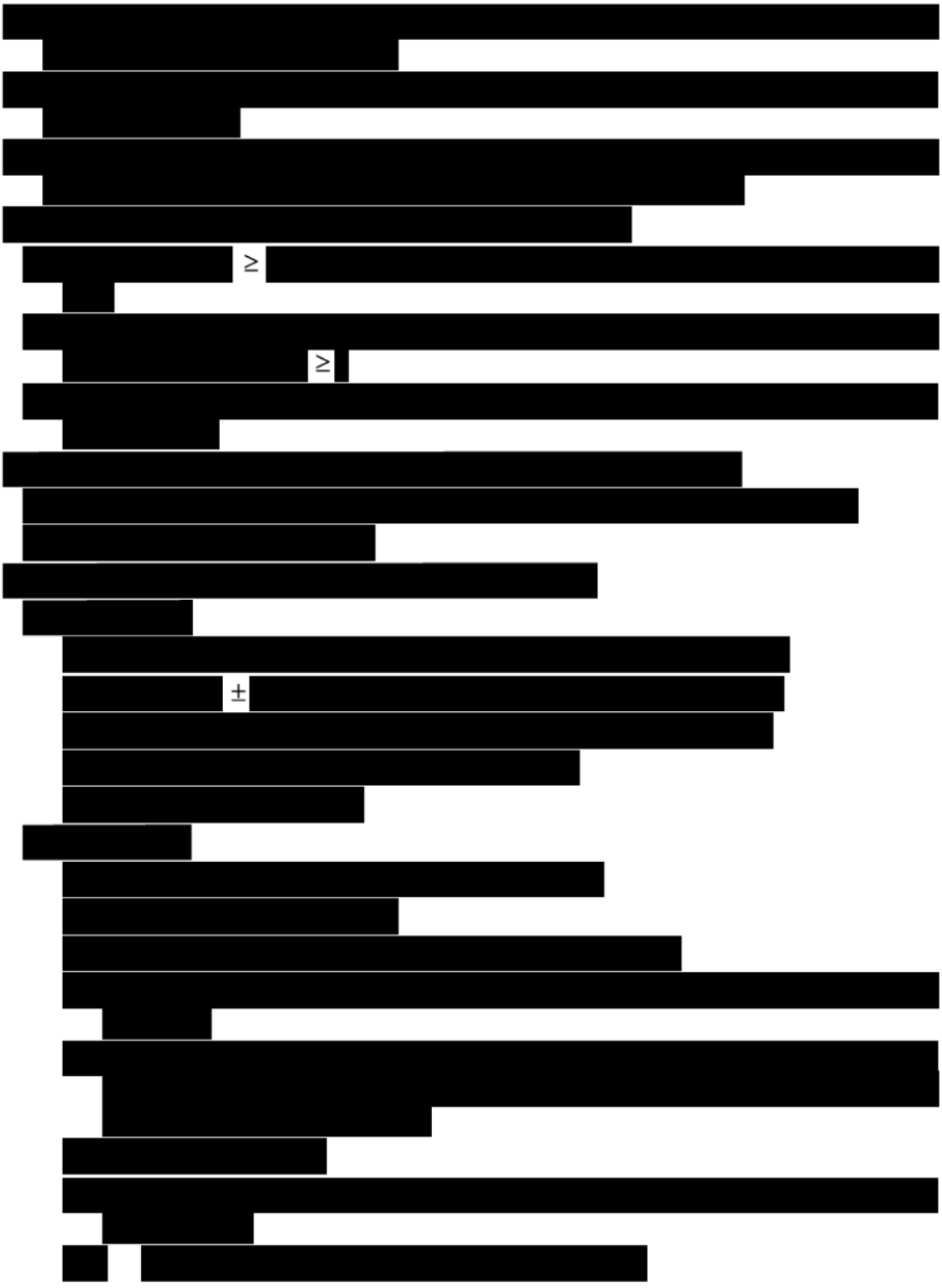
Changes to the Protocol

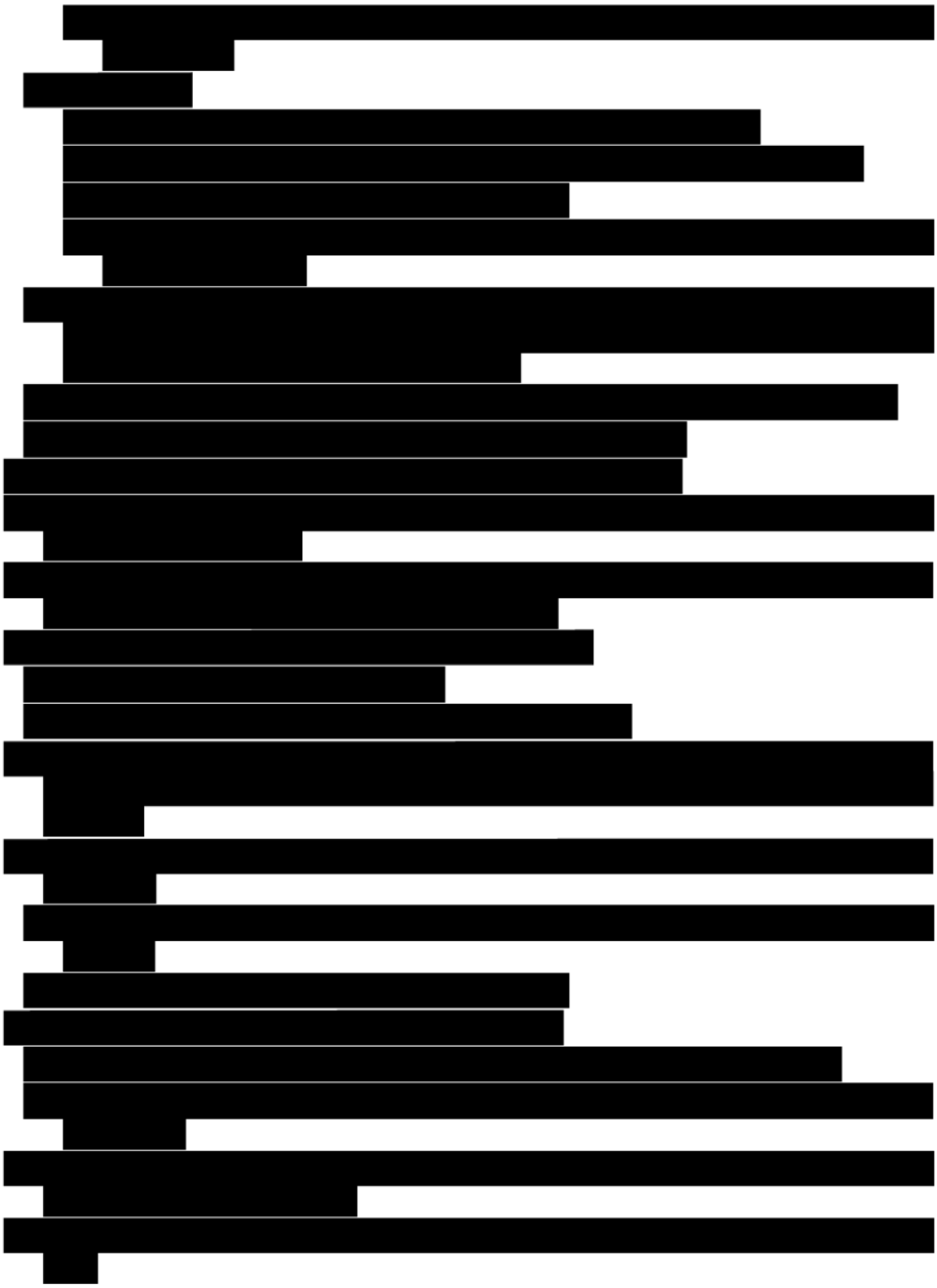
1) **Title page:** Hesham Mohamed is now only listed once as both study director and central medical monitor
2) **Synopsis:**
   a) Investigational Products: Added treatment failure as a reason for withdrawal
   b) Figure Caption: changed "into treatment" to "prior to molecular test date"
   c) Changed wording of "treatment compliance" to "treatment adherence"
   d) Added MMAS-8 as a metric for compliance and deleted patient diary
   e) Added Unknown as a category for Sokal score
   f) "Will require enrollment of 600 patients" changed to "screening of 600 patients."
3) **Document History:** Amendment 01 added to study history
4) **Section 2.3 Informed Consent**: removed patient proxy language

[redacted]

6) **Section 3.3.1 Inclusion Criteria,** Subsection 2a) **Target Population:** Added statement allowing transient dose adjustment of imatinib for AEs
7) **Section 3.3.2 Exclusion Criteria** Subsection 2) Medical History and Concurrent Disease, Subsection iv: Removed 450 msec from definition of prolonged QTC interval
8) **Section 3.5 Discontinuation of Subjects from Study Treatment:**
   a) Treatment failure added as a reason for discontinuation
   b) "Who in treatment failure (per ELN2009)" added to NOTE

[redacted]





[redacted]

Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board / Ethics Committee, unless agreed otherwise with BMS.

Protocol Number: CA180399
IND Number: 66,971
Ex-US Non-IND
EUDRACT Number 2011-006181-41
Date: 20-Feb-2013

Protocool CA180399: AN OPEN LABEL, RANDOMIZED (2:1) PHASE 2B STUDY OF DASATINIB VS. IMATINIB IN PATIENTS WITH CHRONIC PHASE CHRONIC MYELOID LEUKEMIA WHO HAVE NOT ACHIEVED AN OPTIMAL RESPONSE TO 3 MONTHS OF THERAPY WITH 400 MG IMATINIB

Amendment Number 02
Site Number: All

Study Director/Central Medical Monitor
Hesham Mohamed MD

This protocol amendment contains information that is confidential and proprietary to Bristol-Myers Squibb (BMS).

This amendment must be maintained with the referenced protocol.

[redacted]

Changes to the Protocol:

1. Cover page:
   a) Required language added to reflect Amendment 02 and Revised Protocol.
   b) Ex-US-Non IND and BMS address in Belgium added per new model document.
2. Document History: Added information to specify and date Amendment 02 and Revised protocol.
3. Synopsis:
   a) Study population was corrected to indicate that up to 6 months rather than 3 months are allowed between diagnosis and start of treatment with imatinib.
   b) Interim analysis section added.

[redacted].

5. Section 1.3.1 Primary Objective: Minor editorial change.

[redacted]

7. Section 3.3.2, Exclusion Criteria 1) Target Disease Exceptions d): Added two mutations to exclusion criteria if known at screening.
8. Section 3.3.2, Exclusion Criteria 4) Allergies and Adverse Drug Reactions: Subjects with known hypersensitivity to excipients of dasatinib are excluded.
9. Section 3.5, Discontinuation of Subjects from Treatment: Study: Study drug should be discontinued if pulmonary arterial hypertension is confirmed.
10. Section 3.6, Post Treatment Study Follow up: New section with subsections added to comply with requirement of updated model document.

[redacted]

c) Consent for and sample for sub-studies deleted as these studies are no longer an option in this protocol.

d) Patient reported Outcomes: Note added to clarify timing of assessments

[redacted]

16. Section 5.3 Safety Assessments

a) ECG assessment timing clarified.

b) ECG and/or echocardiogram required for patients who cross over to dasatinib, if two or more months have elapsed since last ECG or echocardiogram.

[redacted]

22. Section 7 Data Monitoring Committee and Other External Committees; Additional detail added to specify composition of the independent monitoring committee, their function, data to be examined, and the schedule of the data review.

[redacted]

26. Section 11, Abbreviations; Independent Data Monitoring Committee (IDMC) added.

Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board / Ethics Committee, unless agreed otherwise with BMS.

Protocol Number: CA180399
IND Number: 66,971
EUDRACT Number 2011-006181-41
Date: 09-Oct-2013

Protocol CA180399: AN OPEN LABEL, RANDOMIZED (2:1) PHASE 2B STUDY OF DASATINIB VS IMATINIB IN PATIENTS WITH CHRONIC PHASE CHRONIC MYELOID LEUKEMIA WHO HAVE NOT ACHIEVED AN OPTIMAL RESPONSE TO 3 MONTHS OF THERAPY WITH 400 MG IMATINIB

Amendment Number 05
Site Number: All

Study Director/Central Medical Monitor
Hesham Mohamed MD
[redacted]

This protocol amendment contains information that is confidential and proprietary to Bristol-Myers Squibb (BMS).

This amendment must be maintained with the referenced protocol.

[redacted]

Changes to the Protocol:

[redacted]

3. Section 3.3.1 Inclusion Criteria, 3) Age and Reproductive Status: Criteria in this section have been reordered to accommodate standardization across brand protocols.
   a) Criterion b) Acceptable methods of contraception changed and length of time that contraception must be used changed and specified.
   b) Criterion b) Window for baseline pregnancy test changed to 24 hours.
   c) Criterion d) Specifies requirement for contraception for women of child bearing potential (WOCBP)
   d) Criterion e) Specifies requirement for contraception for fertile sexually active men and specifies acceptable methods of contraception to be used in the study.
   e) Criterion f) New criterion that exempts azoospermic males and WOCBP who are continuously not heterosexually active from requirement to use contraception. However, WOCPB in this category are required to abide by protocol requirements for pregnancy testing.

4. Section 3.3.2 Exclusion Criteria 2) Medical History and Concurrent Disease b) Uncontrolled or significant cardiovascular disease
   a) iii) example of significant ventricular arrhythmias
   b) vi) clarification of unstable angina
   c) viii) uncontrolled hypertension defined
5. Section 3.3.3 Women of Childbearing Potential: Section rewritten to define and specify women of childbearing potential.

[redacted]

8. Section 5.2 Study Materials: Home pregnancy and Pregnancy Log added.
9. Section 5.8.1.2 Bone Marrow: Section rewritten for clarification.
10. Section 5.8.1.4 Pregnancy Test: Section rewritten to comply with new regulations on monthly testing.
11. Section 6.4 Pregnancy: Section was made consistent with new BMS directive on pregnancy and contraception.

[redacted]

Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board / Ethics Committee, unless agreed otherwise with BMS.

Protocol Number: CA180399
IND Number: 66,971
EUDRACT Number 2011-006181-41
Date: 07-May-2015

Protocol CA180399: AN OPEN LABEL, RANDOMIZED (2:1) PHASE 2B STUDY OF DASATINIB VS IMATINIB IN PATIENTS WITH CHRONIC PHASE CHRONIC MYELOID LEUKEMIA WHO HAVE NOT ACHIEVED AN OPTIMAL RESPONSE TO 3 MONTHS OF THERAPY WITH 400 MG IMATINIB

Amendment Number 06
Site Number: All

Study Director/Central Medical Monitor
Hesham Mohamed MD
[redacted]

This protocol amendment contains information that is confidential and proprietary to Bristol-Myers Squibb (BMS).

This amendment must be maintained with the referenced protocol.

[redacted]

Changes to the Protocol:

1. Throughout the protocol, the 2013 version of the European Leukemia Net (ELN) criteria replaces the 2009 version.
2. Throughout the protocol, FISH has been changed to FISH (peripheral blood) or FISH (PB)
3. Title page. BMS Study Director: Title change.

[redacted]

[redacted]

15. Section 3.3.1 Inclusion Criteria 2. Target Population criteria a) and b): Inclusion requirements that specify acceptable interruptions of treatment with imatinib specified.
16. Section 3.3.2 Exclusion Criteria 1. Target Disease Exceptions: b) Clarification added to address eligibility of patients with no evidence of clonal evolution.
17. Section 3.3.2 Exclusion Criteria, 2. Medical History and Concurrent Diseases d) Exclusion of subjects with pleural or pericardial effusions at randomization rather than at study entry.
18. Section 3.4.1, Prohibited and/or Restricted Treatments: Paragraph added as reference to drugs associated with QTc prolongation and Torsade De Pointes.

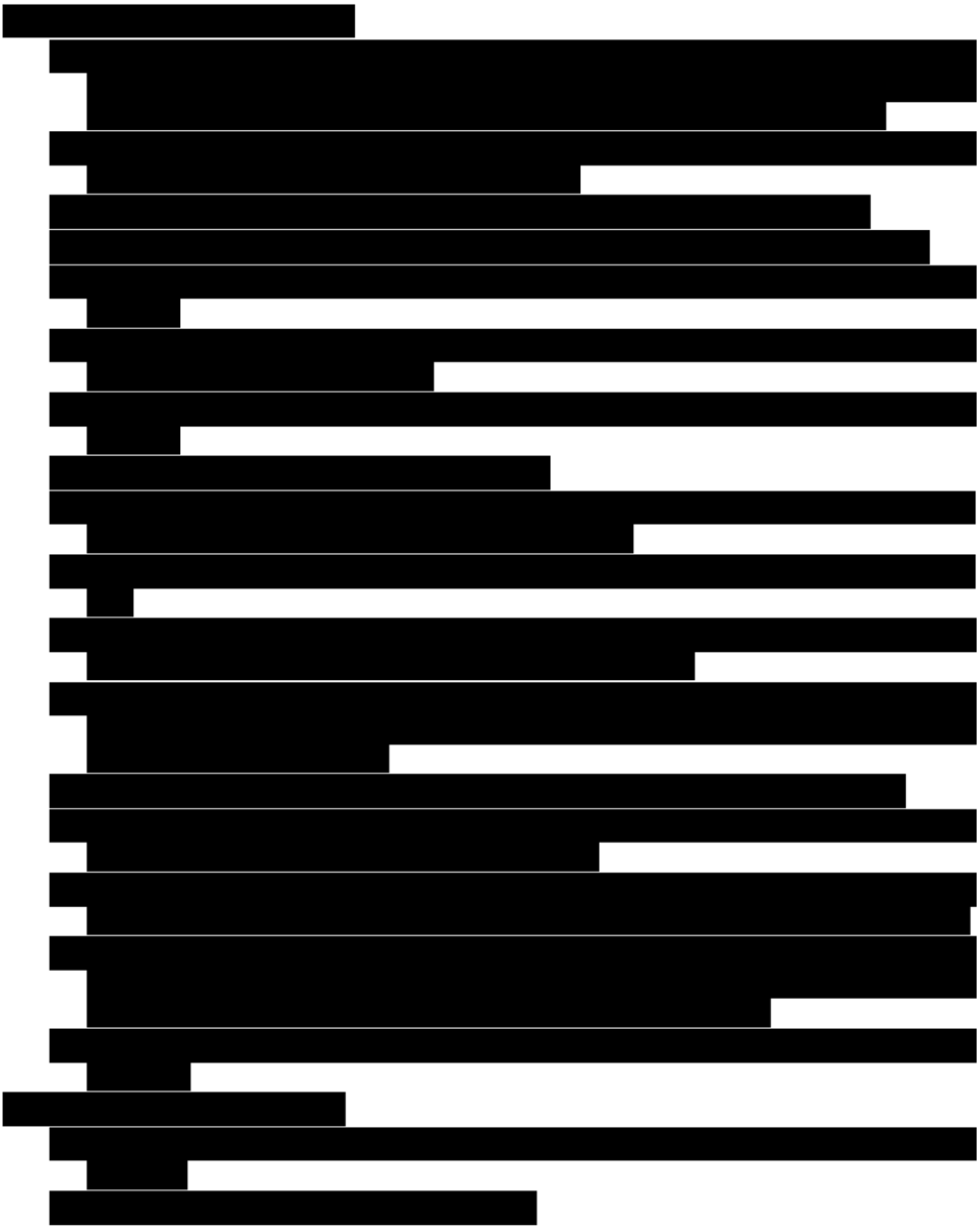
[redacted]

44. Section 7 Data Monitoring Committee and Other External Committees
    a) acronym expansion for IDMC revised to delete the word "independent"
    b) Further information on IDMC is provided in the charter for the IDMC.

[redacted]

47. Section 8.3.2 Secondary Endpoint(s)
    a) Rates of MMR, MR4.5, MR4 at 6, 12, 15, 18, 24, 36 and 48 deleted from secondary endpoints.
    b) Rates of CCyr and MCyr at months 6, 12, and 18 deleted.
    c) Time to MMR added as a secondary endpoint.
    d) Time to MR4-5 added as a secondary endpoint.
    e) Time to and duration of MMR, MR4.5, MR4 and CCyR deleted as a secondary endpoint.

[redacted]



[redacted]

Protocol Number: CA180399
IND Number: 66,971
EUDRACT Number 2011-006181-41
Date: 22-Apr-2016

Protocol CA180399: AN OPEN LABEL, RANDOMIZED (2:1) PHASE 2B STUDY OF DASATINIB VS IMATINIB IN PATIENTS WITH CHRONIC PHASE CHRONIC MYELOID LEUKEMIA WHO HAVE NOT ACHIEVED AN OPTIMAL RESPONSE TO THREE MONTHS OF THERAPY WITH 400 MG IMATINIB

Amendment Number 07
Site Number: All

Study Director/Central Medical Monitor
Hesham Mohamed MD

This protocol amendment contains information that is confidential and proprietary to Bristol-Myers Squibb (BMS).

This amendment must be maintained with the referenced protocol.

[redacted]

Changes to the Protocol:

[redacted]

3. Section 3.3.1 Inclusion Criteria, 3. Age and Reproductive Status:
   a) Criterion e): Text that specifies contraception methods deleted; replaced by Appendix 10.
   b) Criterion f): All male subjects whose partners are women of childbearing potential (WOCBP) are now required to use condoms, including male subjects who are azoospermic.

4. Section 3.3.2 Exclusion Criteria, 2. Medical History and Concurrent Disease a): A subsection has been added (i) to specify that subjects who have positive serology for Hepatitis-B (HBV) can enroll if all other eligibility criteria are met.
5. Section 4.6.1 Destruction of Study Drug: This section has been modified to align with program-wide procedures.

[redacted]

Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board/Ethics Committee, unless agreed otherwise with BMS.