Official Title of Study:

Continuing Treatment for Subjects Who Have Participated on a Prior Protocol Investigating Dasatinib

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Clinical Protocol CA180597

Continuing Treatment for Subjects Who Have Participated on a Prior Protocol Investigating Dasatinib

Revised Protocol Number: 01
Incorporates amendment(s) 01

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to BMS or promptly destroy it. All other rights reserved. References to BMS in this protocol may apply to partners to which BMS has transferred obligations, 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.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 01	19-Apr-2016	Incorporates Amendment(s) 01
Amendment 01	19-Apr-2016	This amendment: 1) adds testing for Hepatitis B virus (HBV) and 2) updates recommendations for methods of contraception and reemphasizes the need for contraception.
Original Protocol	20-Oct-2014	Not applicable

SYNOPSIS

Clinical Protocol CA180597

Protocol Title: Continuing Treatment for Subjects Who Have Participated on a Prior Protocol Investigating Dasatinib

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Subjects will receive dasatinib by oral administration at the last dose and schedule that they had been receiving in the previous clinical trial.

Study Phase: Continuation Phase 2 Roll-Over Protocol

Research Hypothesis: No formal research hypothesis will be tested.

Objectives:

Primary Objective: To provide dasatinib treatment to patients who have participated on a prior protocol investigating dasatinib.

Secondary objective: To monitor the safety and tolerability of dasatinib.

Study Population:

- Subjects who are currently receiving dasatinib therapy on another clinical trial that is ending.
- Inclusion criteria:
  a) Participated in and completed a previous dasatinib protocol (including but not limited to CA180056, CA180363 or CA180227) and is deemed by the investigator to be deriving benefit from dasatinib as defined by the previous protocol.
  b) Receiving dasatinib at the time of signature of informed consent.
- Exclusion criteria:
  a) All patients previously discontinued from a dasatinib study for any reason.

Study Assessments:

- Eligibility, safety (AEs and SAEs) and dosing assessments will be collected
- Efficacy assessments will not be collected on study but should be performed per standard of care.

Statistical Considerations:

Sample Size: Sample size is not based on statistical power considerations. This dasatinib rollover protocol will enroll any eligible patient including but not limited to subjects on treatment in studies CA180056, CA180363 or CA180227.

Endpoints: In this study, endpoints will include number of patients who received dasatinib and duration of treatment, all SAEs and AEs will be collected.

Analyses: Data will be analyzed descriptively; details will be provided in the statistical analysis plan.

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1 INTRODUCTION AND STUDY RATIONALE

Dasatinib (BMS-354825) is a potent, broad-spectrum adenosine triphosphate (ATP) competitive inhibitor of multiple oncogenic tyrosine kinases including BCR-ABL, SRC, c-KIT, platelet-derived growth factor receptor, and ephrin receptor kinases.[1,2] Overexpression or activation of these kinases plays critical roles in the etiology of various cancer types, as well as the malignant behavior associated with these diseases, such as unregulated proliferation and metastasis. Dasatinib has been approved for treatment of adults with chronic myeloid leukemia (CML) or Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) resistant or intolerant to imatinib or newly diagnosed chronic phase CML (CP-CML).

Several studies in adults with Ph+ leukemias and solid tumors were successful in generating a range of safe and effective dose schedules for the administration of dasatinib. In CML, a Phase 1 study provided evidence of efficacy of dasatinib as demonstrated by hematologic and cytogenetic responses in all disease stages. Based on preclinical data and results from Phase 1, the dose of 70 mg twice daily (BID) was selected for the initial Phase 2 studies. Five Phase 2 studies (START CA180005, -006, -013, -015 and, -017) were conducted to further assess the efficacy and the safety profile of dasatinib.[3,4,5,6,7] Based on the Phase 1 and Phase 2 studies, dasatinib was approved by the US Food and Drug Administration (FDA) in June 2006 for use in subjects with all phases of CML and Ph+ ALL who were resistant to or intolerant of imatinib. Two Phase 3 trials in CP-CML (CA180034), advanced phase CML and Ph+ ALL (CA180035) provided evidence that a lower total daily dose (100 mg) given once daily maintains the same efficacy with greater subject tolerability than the 70 mg BID dose.[8,9] Another Phase 3 trial (CA180056) showed statistically significant improvement in complete cytogenetic responses at 12 months with dasatinib compared to imatinib.[10] This study led to the approval of dasatinib in the treatment of newly diagnosed CP-CML.

In addition to the trials conducted in Ph+ leukemias, five BMS-sponsored Phase 1 studies and nine Phase 2 studies were conducted to explore the safety and efficacy across various solid tumor types including advanced/refractory solid tumors (CA180003, CA180021, CA180058), breast cancer (CA180004, CA180059, CA180088, CA180158, CA180185, CA180261), prostate cancer (CA180085, CA180086, CA180227), glioblastoma (CA180274), pancreatic cancer (CA180375) and advanced non-small cell lung cancer (CA180385). Finally, one Phase 3 study was pursued in metastatic castration-resistant prostate cancer, mCRPC (CA180227).[11] A variety of other BMS and investigator-sponsored trials in hematologic malignancies and solid tumors have also been conducted in adults.

The safety profile of dasatinib is mostly characterized by fluid retention and myelosuppression. Incidence rates of fluid retention-related events (including pleural effusion, congestive heart failure, pericardial effusion, and pulmonary edema), pulmonary arterial hypertension (PAH), and cytopenias (including neutropenia, thrombocytopenia, and anemia) continue to be of special interest.[12] The safety data generated in subjects with solid tumors has not identified any new

safety risks compared to those in subjects with CML or Ph+ ALL. Currently, dasatinib is not approved for the treatment of any solid tumor types in adults or in children for any indication.

1.1 Study Rationale

This is an open-label, continuation roll-over protocol that will provide dasatinib to subjects who are currently receiving this therapy on another clinical trial (including but not limited to CA180056, CA180363 or CA180227). This study will obtain safety follow up of enrolled subjects after completion of other dasatinib studies.

1.2 Research Hypothesis

No formal research hypothesis will be tested.

1.3 Objectives(s)

1.3.1 Primary Objectives

To provide dasatinib treatment to subjects who have participated on a prior protocol investigating dasatinib.

1.3.2 Secondary Objectives

To monitor the safety and tolerability of dasatinib.

1.4 Product Development Background

Dasatinib was first approved 28-Jun-2006 by the US FDA for the treatment of adult subjects with CML or Ph+ ALL who are resistant or intolerant to imatinib. Dasatinib was subsequently approved in other countries and is marketed worldwide for the indications below in over 60 international countries including in the EU, Japan, and Canada.

- Dasatinib is indicated for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase CML with resistance to or intolerance of prior therapy including imatinib.
- Dasatinib is indicated for the treatment of adults with Ph+ ALL with resistance to or intolerance of prior therapy.
- Dasatinib is indicated for the treatment of adults with newly diagnosed CP-CML.

1.5 Overall Risk/Benefit Assessment

Dasatinib has proven therapeutic value in CML and is considered to be a standard of care. The safety profile of dasatinib is mostly characterized by fluid retention, gastrointestinal toxicities (nausea and diarrhea), fatigue and myelosuppression. The fluid retention seen was most commonly: pleural or pericardial effusions, superficial edema, pulmonary hypertension, and congestive heart failure. As referred to earlier, results of a Phase 3 (dose-optimization) study led to the approval of 100 mg QD dasatinib in patients with CP-CML with resistance, intolerance, or suboptimal response to imatinib. A 4-year follow-up of these patients confirmed 100 mg QD as the best-tolerated dose, with few Grade 3/4 side effects. In a Phase 3 dose-optimization study in patients with advanced phase CML and Ph+ ALL (median duration of treatment of 14 months

for AP-CML, 3 months for myeloid blast CML, 4 months for lymphoid blast CML and 3 months for Ph+ ALL), fluid retention (pleural effusion and pericardial effusion) was reported less frequently in patients treated with dasatinib 140 mg once daily than in those treated with 70 mg twice daily. Based on these collective data, 100 mg QD and 140 mg QD have been selected as the most appropriate doses in this study for CP-CML and AP-CML patients respectively. Dasatinib at both doses has a well described safety profile with most subjects experiencing Grade 1 - 2 AE that can be managed with dose interruptions and/or reductions.

The safety data generated in subjects with solid tumors and pediatric subjects have not identified any new safety risks, the safety profile is consistent with that observed with the hematological malignancies. Therefore, subjects that appear to be deriving benefit from the continued treatment of dasatinib with acceptable toxicity may continue treatment, even though no definitive efficacy has been demonstrated in solid tumor program.

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

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 Harmonisation (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 (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

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

Investigators must:

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

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

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

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

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This study is an open-label, continuation roll-over study of dasatinib for subjects who are currently receiving dasatinib therapy on another clinical trial that is ending. There is no target number of subjects to be enrolled in this study. It is estimated that ≤50 subjects will be enrolled Each subject will continue to receive dasatinib at the last dose and schedule received on the previous study. Safety and tolerability information will be collected through laboratory testing and adverse event reporting (adverse events will be assessed by the CTCAE version 4.0).

Subjects will continue on study until the Investigator deems that the subject is not benefiting from treatment. Reasons for discontinuation from study may include progression of disease, unacceptable toxicity or subject withdrawal/discontinuation from the study. The study will continue until all subjects have discontinued study medication or until all subjects are treated for up to 2 years.

All subjects will be followed for a minimum of 30 days after the last dose of study drug therapy. If study related toxicities are present at the End of Treatment visit, additional follow-up visit(s) are required until all study related toxicities resolve to baseline or to CTC Grade 1, stabilize or are deemed irreversible.

3.2 Post Study Access to Study

At the end of the study/Period, treatment with study drug for up to 2 years after enrollment, BMS will not continue to provide BMS supplied study drug to subjects/investigators unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

3.3 Study Population

The study population includes subjects who are currently receiving dasatinib therapy on another dasatinib clinical trial that is ending.

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

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Subjects able to provide written informed consent

2. Target Population

a) Participated in and completed a previous dasatinib protocol (including but not limited to CA180056, CA180363 or CA180227) and is deemed by the investigator to be deriving benefit from dasatinib as defined by the previous protocol.

b) Receiving dasatinib at the time of signature of informed consent

c) Subject Re-enrollment: This study does not permit the re-enrollment of a subject who has discontinued the study as a pre-treatment failure.

3. Age and Reproductive Status

a) Males and Females, ages 18 and older

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 for the duration of treatment with study, dasatinib plus 30 days (duration of ovulary cycle) for a total of 30 days post-treatment completion.

e) Males 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 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% 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 described in Appendix 4.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) All patients previously discontinued from a dasatinib study for any reason

2. Medical History and Concurrent Diseases

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

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.

3. Physical and Laboratory Test Findings

Not applicable

4. Allergies and Adverse Drug Reaction

a) History of allergy to dasatinib

5. 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
c) Dementia or serious psychiatric condition that may compromise the informed consent process and increase the risks associated with study participation.

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, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/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 judgement 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

Continued co-administration of additional anticancer therapy, other than prohibited therapies below, is allowed as per previous protocol. No additional anticancer therapy may be started on study.

3.4.1.1 Medications that Prolong QT Interval

Medications associated with QT interval prolongation that are prohibited while subjects are on active therapy with dasatinib during 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.

Ideally, subjects enrolled in this study should not begin taking other medications known to prolong the QT interval. A website and further information on 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 listed above which are 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.

3.4.2 Other Restrictions and Precautions

Restricted therapies are not prohibited, but are not recommended; therefore, the following are permitted with caution if clearly medically indicated.

3.4.2.1 H2-Agonists, PPIs, and Antacids

The concomitant use of dasatinib and a histamine (H2) antagonist (eg, famotidine), proton pump inhibitor [PPI (eg, omeprazole)], or aluminium hydroxide/magnesium hydroxide (eg, Maalox®)

may reduce the exposure to dasatinib. Thus, H2 antagonists and PPIs are not recommended (but are not prohibited) and aluminium hydroxide/magnesium hydroxide products should be administered at least 2 hours before or after dasatinib.

3.4.2.2 Antiplatelet Agents and Anticoagulants

Caution should be exercised if subjects are required to take medications that inhibit platelet function (ie, anticoagulant and antiplatelet agents). Further, anticoagulants should be avoided in the setting of Grade 3 or 4 thrombocytopenia, while subjects are on active dasatinib treatment.

Based on pre-clinical and 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. As a precaution treatment with dasatinib should not be given 24 hours prior to and after such procedures.

3.4.2.3 Agents Affecting CYP3A4

Dasatinib is predominantly metabolized by the CYP3A4 pathway. Strong and moderately-potent inhibitors of CYP3A4 should be avoided in combination with dasatinib if not clearly indicated, as they may increase dasatinib concentrations unpredictably. Substantial quantities of grapefruit, pomegranate and Seville (blood) orange juices may also inhibit CYP3A4. Refer to Appendix 2 for a list of agents affecting the CYP enzyme system.

CYP3A4 inducers (eg, rifampicin) may decrease the concentration of dasatinib and should be used with caution when administered concurrently. Alternative agents with less enzyme-inducing potential should be considered if anticonvulsant therapy is indicated.

There is no restriction on agents metabolized by CYP3A4, but other CYP3A4 substrates known to have a narrow therapeutic index (eg, cyclosporine) should be administered with caution in subjects receiving dasatinib.

3.5 Discontinuation of Subjects following any Treatment with Study Drug

Subjects will continue on study until progression or unacceptable toxicity or until subject withdrawal/discontinuation from the study.

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

- Subject's request to stop study treatment
- 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
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Disease progression which, in the investigator's opinion, precludes the subject's continued participation in the study

- In the opinion of the investigator, continued participation in the study is not in the best interest of the subject
- QTcF value > 530 msec
- Subject eligible and willing to undergo stem cell transplant.
- Non-compliance by the subject with the requirements of the protocol, treatment or monitoring
- Two years after being enrolled in this study, or until the subject can obtain dasatinib from a government sponsored or private health program, whichever comes first.

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

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

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

3.6 Post Study Drug Study Follow up

All subjects will be followed for a minimum of 30 days after the last dose of study drug therapy.

3.6.1 Withdrawal of Consent

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

3.6.2 Lost to Follow-Up

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

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

4 STUDY DRUG

Study drug includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

Table 4-1: Study Drugs for CA180597

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
Dasatinib Film-coated Tablet	20 mg	30 tablets per bottle	Open Label	film coated tablets, biconvex, round, white to off-white in appearance with “20” or “BMS”debossed on one side and “527” on the other side	15° to 25°C (59° to 77°F)
Dasatinib Tablet	50 mg	30 tablets per bottle	Open Label	film coated tablets, biconvex, oval, white to off-white in appearance with “50” or “BMS” debossed on one side and “528” on the other side	15° to 25°C (59° to 77°F)

4.1 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.

Dasatinib 20 mg and 50 mg film-coated tablets (see description in Table 4-1).

4.2 Non-investigational Product

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

Not applicable for this study.

4.3 Storage 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.

Study drug not supplied by BMS will be stored in accordance with the package insert.

Investigational product documentation (whether supplied by BMS or not) 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).

4.4 Method of Assigning Subject Identification

Each site will be assigned a new site number by BMS at the start of the study.

Once a subject has been confirmed as eligible by the investigator, a subject number will be assigned by the site. The site will assign the subject numbers sequentially for that site, starting with the number [redacted].

This unique subject number and the newly assigned site number must be recorded on the CRF and on all further documentation and correspondence referring to this particular subject.

The protocol and subject number from the prior BMS dasatinib protocol, under which the subject was receiving dasatinib prior to enrollment in the current protocol, will also be recorded on the screening CRF pages.

Once informed consent has been obtained, the investigator (or designee) will register the subject by transmitting a copy of the completed enrollment worksheet (registration form) by facsmile (fax) or email to the number/email address listed on the cover page. The following information is required for registration.

4.5 Selection and Timing of Dose for Each Subject

Dasatinib will be administered at the last dose and schedule received on the previous study. Subjects may adjust the time they take dasatinib as long as they take the drug approximately every 24 hours. Dasatinib tablets should be taken once per day at the same time with or without food. Dose modifications for dasatinib should be made when dasatinib related toxicity is suspected (outlined below in Table 4.5-1).

Table 4.5-1: Dose Modification Guidance for Dasatinib Related Toxicities

Toxicity	Action to be taken with dasatinib
Grade 3 drug-related hematologic toxicity	Interrupt until ANC ≥ 1.0 x 10^9/L and platelets ≥ 50 x 10^9/L. Resume treatment with dasatinib at the original starting dose if recovery occurs in ≤ 7 days. If > 7 days, resume dasatinib at dose level 80 mg QD. For second episode, resume at dose level 50 mg QD.
Grade 4 drug-related hematologic toxicity	Interrupt until ANC ≥ 1.0 x 10^9/L and platelets ≥ 50 x 10^9/L. Resume treatment with dasatinib at dose level 80 mg QD if recovery occurs in ≤ 7 days. For second episode, reduce dose to dose level 50 mg QD.
Grade 1 pleural effusion	Interrupt until resolved and resume at same dose level. For second episode, reduce to dose level 80 mg QD.
Grade ≥ 2 pleural effusion	Interrupt until resolved and then resume at dose level 80 mg QD. For second episode, resume at dose level 50 mg QD.
Grade ≥ 3 LFTs	Interrupt until ≤ Grade 1or baseline and resume dasatinib.
QTc/f > 500 msec, confirmed by repeat ECG.	Interrupt until Grade ≤ 1, Eliminate drugs that prolong QTc/f, Supplement K, Mg; Consider monitored rechallenge. NOTE: Subject should be discontinued in the event of QTc/f > 530 msec.
LVEF Grade 2 (or decrease by > 10% from baseline), confirmed by repeat Echo	Interrupt until ≤ Grade 1 or baseline and resume dasatinib at same dose. For second episode, reduce to dose level 80 mg QD. If Grade ≥ 3, reduce to dose level 80 mg QD.
Other Grade 3 - 4 non hematologic event (eg, vomiting) despite adequate medical intervention	Hold until ≤ Grade 1 or baseline and resume at dose level 80 mg QD

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the subject's medical record and eCRF.

4.8 Destruction of Study Drug

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

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

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

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

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

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

4.9 Return of Study Drug

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

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local,

and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

Arrangements for the return of study drug will be made by the responsible Study Monitor.

4.10 Retained Samples for Bioavailability / Bioequivalence

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

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline (CA180597)

Procedure	Screening[a]	During Treatment Visit 1	Every 6 months	Every 12 months	End of Treatment Visit X	30 Days Follow-Up Phone Call Visit	Notes
Eligibility Assessments							
Informed consent	X						
Inclusion/Exclusion Criteria	X						
Medical History	X						
Safety Assessments							
Physical Examination		X[b]		X	X		
Vital Signs		X[b]		X	X		Heart rate, blood pressure, temperature, weight, respiratory rate
Serious Adverse Event Assessment		X				X	
Adverse Events Assessment & Concomitant Medication		X				X	
Serum Chemistry		X[b]	X		X		BUN, creatinine, ALT, AST, total bilirubin
CBC with differential and platelets		X[b]	X		X		

Table 5.1-1: Screening Procedural Outline (CA180597)							
Procedure	**Screening[a]**	**During Treatment Visit 1**	**Every 6 months**	**Every 12 months**	**End of Treatment Visit X**	**30 Days Follow-Up Phone Call Visit**	**Notes**
Pregnancy Test		<--------> Monthly					Need to be done monthly. Home pregnancy test kits provided to WOCBP subjects to perform pregnancy test between visits and record result in log book For WOCBP only
Review Contraception requirements		X			X		
Hepatitis B serologic testing	X	See Note					Hepatitis B surface antigen (HBsAg) and antibody to Hepatitis B core antigen (also known as total hepatitis B core antibody; anti-HBc The test has to be done at screening or once during the study (for subjects already treated)
Study Drug							
Dispense Study Drug		X	X				

[a] Screening visit will take place the same day as Visit 1.

[b] Record information from EoT visit of parent study on CRF

5.1.1 Retesting During Screening or Lead-in Period

Not applicable.

5.2 Study Materials

The following will be distributed to the sites:

- Dasatinib Investigator Brochure (current version 14, updated when available).
- Clinical supplies.
- Pregnancy tests log.

The site will provide materials for tests performed locally (ie, clinical laboratory tests).

5.3 Safety Assessments

The schedule of study visits, assessments and procedures is provided in Table 5.1-1. Informed consent must be obtained prior to any study required procedures that would not have been performed as part of normal subject care (Section 2.3). While collection of safety laboratory data will only occur 6 months, subject should receive routine monitoring for safety and efficacy as per standard of care. In addition, for WOCBP, monthly pregnancy testings need to be performed.

HBV Serology

Although subjects with acute 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 Imaging Assessment for the Study

Not applicable.

5.4 Efficacy Assessments

Efficacy assessments will not be collected on study but should be performed per standard of care.

5.5 Biomarker Assessments

Not applicable.

5.6 Outcomes Research Assessments

Not applicable.

5.7 Other Assessments

Not applicable.

5.8 Results of Central Assessments

Not applicable.

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 study drug 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 study drug, whether or not considered related to the study drug.

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

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

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

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

6.1 Serious Adverse Events

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

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).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols).

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited 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). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only

intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs 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): Refer to 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. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

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 study drug, 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 Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours and in accordance with 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.

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 SAE reporting procedures described in Section 6.1.1.

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

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

6.5 Overdose

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

6.6 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)
   AND
2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
   AND
3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.7 Other Safety Considerations

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Not applicable.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

Sample size is not based on statistical power considerations. This dasatinib rollover protocol will enroll any eligible subject including but not limited to subjects on treatment in studies CA180056, CA180363 or CA180227.

8.2 Populations for Analyses

The following dataset will be used in this study:

– All treated subjects: all subjects who received at least one dose of dasatinib.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

Number of subjects who received dasatinib treatment and duration of treatment will be collected.

8.3.2 Secondary Endpoint(s)

In this study, all SAEs and AEs will be collected.

8.3.3 Exploratory Endpoint(s)

Not applicable.

8.4 Analyses

Detailed analysis description will be provided in the statistical analysis plan. Analysis will be conducted when all subjects have discontinued the study.

8.4.1 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be tabulated for all treated subjects by disease type. Analysis by dose will be performed if deemed appropriate.

8.4.2 Efficacy Analyses

Not applicable.

8.4.3 Safety Analyses

Analysis of safety data will be performed on all treated subjects by disease type. Analysis by dose will be performed if deemed appropriate. Data will be analyzed descriptively. Adverse events and other symptoms will be graded according to the NCI. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

8.4.4 Pharmacokinetic Analyses

Not applicable.

8.4.5 Biomarker Analyses

Not applicable.

8.4.6 Outcomes Research Analyses

Not applicable.

8.4.7 Other Analyses

Not applicable.

8.5 Interim Analyses

Not applicable.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

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

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

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations.

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

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

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

9.1.2 Monitoring

BMS representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

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

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

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

9.1.2.1 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

9.1.3 Investigational Site Training

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

9.2 Records

9.2.1 Records Retention

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

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

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

9.2.2 Study Drug Records

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

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

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

9.2.3 Case Report Forms

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

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

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

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

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

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

9.3 Clinical Study Report and Publications

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

For this single site protocol, the Principal Investigator for the site will sign the clinical study report.

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
Complete Abstinence	If one form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. If two forms of contraception is required, Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. **Expanded definition** Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (e.g., calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ALL	Acute Lymphoblastic Leukemia
ALT	alanine aminotransferase
AP	Accelerated Phase
AST	aspartate aminotransferase
BID, bid	bis in die, twice daily
BMS	Bristol-Myers Squibb
BP	blast phase
BUN	blood urea nitrogen
C	Celsius
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
C1-	chloride
cm	centimeter
CRF	Case Report Form, paper or electronic
Ct	Expected concentration at a certain time, usually at the end of an expected future dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
CYP	cytochrome p-450
D/C	discontinue
dL	deciliter
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eg	exempli gratia (for example)
F	bioavailability
FDA	Food and Drug Administration
g	gram
GCP	Good Clinical Practice

Term	Definition
h	hour
HR	heart rate
HRT	hormone replacement therapy
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IU	International Unit
K+	potassium
kg	kilogram
L	liter
LDH	lactate dehydrogenase
mg	milligram
Mg++	magnesium
min	minute
mL	milliliter
mmHg	millimeters of mercury
µg	microgram
N	number of subjects or observations
Na+	sodium
N/A	not applicable
ng	nanogram
NIMP	non-investigational medicinal products
PO	per os (by mouth route of administration)
QC	quality control
QD, qd	quaque die, once daily
RBC	red blood cell
SAE	serious adverse event

Term	Definition
SOP	Standard Operating Procedures
sp.	species
Subj	subject
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
T-HALF	Half life
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
x g	times gravity

12 REFERENCES

1 Preclinical pharmacology of dasatinib, a SRC protein kinase inhibitor. Bristol-Myers Squibb Company; 2003. Document Control No. 930003300.

2 Further studies on the preclinical pharmacology of dasatinib (BMS-354825), a multi-targeted tyrosine kinase inhibitor. Bristol-Myers Squibb Company. Document Control No. 930012327.

3 BMS-354825, Bristol-Myers Squibb Interim Clinical Study Report for Study CA180005, Dec 2005. BMS Document Control No. 9300013100.

4 BMS-354825, Bristol-Myers Squibb Interim Clinical Study Report for Study CA180006, Dec 2005. BMS Document Control No. 9300013152.

5 BMS-354825, Bristol-Myers Squibb Interim Clinical Study Report for Study CA180013, Dec 2005. BMS Document Control No. 9300013195.

6 BMS-354825, Bristol-Myers Squibb Interim Clinical Study Report for Study CA180015, Dec 2005. BMS Document Control No. 9300011891.

7 BMS-354825, Bristol-Myers Squibb Interim Clinical Study Report for Study CA180017, Dec 2005. BMS Document Control No. 9300011560.

8 Clinical study report for Study CA180034: A randomized two-by-two, multicenter, open-label phase 3 study of BMS-354825 administered orally at a dose of 50 mg or 70 mg twice daily or 100 mg or 140 mg once daily in patients with chronic phase Philadelphia chromosome or BCR-ABL positive chronic myelogenous leukemia who are resistant or intolerant to imatinib mesylate. Six-month Clinical Study Report. Bristol-Myers Squibb Company; 2007. Document Control No. 930020746.

9 Final clinical study report for Study CA180035: A randomized, twoarm, multicenter, open-label Phase III study of BMS-354825 administered orally at a dose of 70 mg twice daily or 140 mg once daily in subjects with chronic myeloid leukemia in accelerated phase or in myeloid or lymphoid blast phase or with Philadelphia chromosome positive acute lymphoblastic leukemia who are resistant or intolerant to imatinib mesylate. Two-year Clinical Study Report. Bristol-Myers Squibb Company; 2008. Document Control No. 930029431.

10 Clinical study report for Study CA180056: An open-label, randomized, multicenter Phase III trial of dasatinib (SPRYCEL®) vs. standard dose imatinib (400 mg) in the treatment of subjects with newly diagnosed chronic phase Philadelphia chromosome positive chronic myeloid leukemia. Bristol-Myers Squibb Company; 2010. Document Control No. 930041803.

11 Final clinical study report for Study CA180227: A randomized double blind Phase 3 trial comparing docetaxel combined with dasatinib to docetaxel combined with placebo in castration-resistant prostate cancer. Bristol-Myers Squibb Company; 2013. Document Control No. 930070027.

[12] BMS-354825 Investigator Brochure, Version #14. Princeton, NJ: Bristol-Myers Squibb; 2005. Report No.: BMS Document Control No. 930003494.

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.

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.

APPENDIX 2 COMMON CYP3A4 SUBSTRATES, INDUCERS, AND INHIBITORS

The following lists describe medications which are common CYP3A4 substrates, inducers and inhibitors. These lists should not be considered all inclusive. Consult individual medication labels for specific information on a compound's propensity for metabolism by CYP3A4. For medication/compounds you do not find in this appendix, please look at the following website to determine if they may be processed through the CYP3A4 pathway (in case of any doubts, **discussion with the BMS Medical Monitor is strongly encouraged**). Refer to: http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm ***or*** http://medicine.iupui.edu/clinpharm/ddis/table.aspx

Common CYP3A4 Substrates (not all inclusive)

Anti-arrhythmics:
quinidine

Antihistamines:
astemizole
chlorpheniramine
terfenidine

Benzodiazepines:
alprazolam
diazepam
dronedarone
midazolam
triazolam

Calcium Channel Blockers:
amlodipine
diltiazem
felodipine
lercanidipine
nifedipine
nisoldipine
nitrendipine
verapamil

Immune Modulators:
Cyclosporine
sirolimus
tacrolimus (FK506)

Macrolide Antibiotics:
clarithromycin
erythromycin
telithromycin
NOT: zithromycin

HIV Antivirals:
darunavir
indinavir
lopinavir
maraviroc
nelfinavir
ritonavir
saquinavir
tipranavir

HMG CoA Reductase Inhibitors:
atorvastatin
cerivastatin
lovastatin
NOT: pravastatin
NOT: Simvastatin

Steroid 6beta-OH:
budesonide
estradiol
fluticasone
hydrocortisone
progesterone
testosterone

Others:
Alfentanyl
aripiprazole
aprepitant
boceprevir
buspirone
cafergot
caffeine
cilostaxol
cisapride
cocaine
conivaptan
dapsone
docetaxel
domperidone
codeine-N-demethylation
darifenacin
dexamethasone
dextromethorphan
dihydroergotamine
eletriptan
eplerenone
ergotamine
everolimus
fentanyl
finasteride
gleevec
haloperidol
irinotecan
LAAM
Lidocaine
lurasidone
methadone
nateglinide
odanestron
pimozide
propranolol
quinine
quetiapine
risperidone
salmetrerol
sildenafil
sorafinib
tamoxifen
taxol
tolvaptan
torisel
trazodone
vardenafil
vincristine
zaleplon
ziprasidon
zolpidem

Strong CYP3A4 Inhibitors	Moderate CYP3A4 Inhibitors	Weak CYP3A4 Inhibitors
≥ 5-fold increase in AUC	≥ 2 but < 5-fold increase in AUC	≥ 1.25 but < 2-fold increase in AUC
atazanavir, boceprevir, clarithromycin, conivaptan, grapefruit juice,(a) indinavir, itraconazole, ketoconazole, mibefradil , nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycins, voriconazole	amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, blood orange juice, pomegranate juice, grapefruit juice,[a] verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo,[b] goldenseal,[b] isoniazid, nilotinib, Oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton

[a] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and is preparation dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).

[b] Herbal product.

Common CYP3A4 Inducers (not all inclusive)

HIV Antivirals:
Efavirenz
nevirapine

Others:
Amprenavir
Aprepitant
armodafinil
barbiturates
bosentan
carbamazepine
echinacea
etravirine
glucocorticoids
modafinil
nafcillin
phenobarbital
phenytoin
rifabutin
rifampin
rufinamide
St. John's wort

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

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

Patients are prohibited from taking medications listed in Category 1: Drugs with Risk of Torsade de Pointes. Caution is warranted when administering BMS-354825 to subjects taking drugs associated with prolongation of QTc listed in Category 2: Drugs with Possible Risk of Torsade de Pointes. A separate study document delineating medications currently listed in Categories 1 and 2 will be provided and updated as necessary.

APPENDIX 4 METHODS OF CONTRACEPTION

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

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

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

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

LESS EFFECTIVE METHODS OF CONTRACEPTION

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

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

UNACCEPTABLE METHODS OF CONTRACEPTION

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