CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-986/S001 & 002

Trade Name: SPRYCEL Tablets

Generic Name: dasatinib

Sponsor: Bristol-Myers Squibb Company

Approval Date: November 8, 2007

Indication: The use of a lower dose of SPRYCEL for the treatment of adults with chronic phase chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy including imatinib mesylate and provide information on the results of a Phase 2 randomized trial of SPRYCEL 70 mg twice daily to imatinib 800 mg daily

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPLICATION NUMBER:

21-986/S001 & 002

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-986/S-001
NDA 21-986/S-002

Bristol-Myers Squibb Company
Attention: Meenal Pai, Pharm. D.
Manager, Global Regulatory Science
5 Research Parkway
P.O. Box 5100, Mailstop 3SIG-3021
Wallingford, CT 06492

Dear Dr. Pai:

Please refer to your supplemental new drug applications dated May 10, 2007, received May 11, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SPRYCEL® (dasatinib) Tablets.

We acknowledge receipt of your submissions dated August 30, 2007; September 6, 11, 20, and 25, 2007; October 8, 10, 16, 19, and 31, 2007; and November 5 and 7 (electronic), 2007.

These supplemental new drug applications (S-001, S-002) provide for the use of a lower dose of SPRYCEL® for the treatment of adults with chronic phase chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy including imatinib mesylate and provide information on the results of a Phase 2 randomized trial of SPRYCEL® 70 mg twice daily or imatinib 800 mg daily.

We completed our review of these applications, as amended. They are approved under the provisions of the accelerated approval regulations (21 CFR 314.510), effective on the date of this letter, for use as recommended in the enclosed labeling text and patient labeling. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert).

Submit content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material.

For administrative purposes, designate this submission "**FPL for approved supplement NDA 21-986/S-001 and NDA 21-986/S-002**." Approval of this submission by FDA is not required before the labeling is used.

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your postmarketing study commitments specified in your submission dated June 27, 2006. These commitments, along with any completion dates agreed upon, are listed below.

1. You have agreed to submit the complete study report and data from the study, CA-180-002, a bicenter, dose escalation study to determine the safety, pharmacokinetics, and pharmacodynamics of BMS-354825 in the treatment of patients with Chronic, Accelerated, or Blast Phase Chronic Myelogenous Leukemia, or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia who have hematologic resistance to Imatinib Mesylate.

   Protocol Submission: 03/2003
   Study Start: 11/2003
   Final Report Submission: 06/2007

2. You have agreed to submit the complete study report (24 months follow-up) and data from the study, CA-180-005, a phase 2 multicenter study of dasatinib (BMS-354825) in subjects with Accelerated Phase Chronic Myeloid Leukemia resistant to or intolerant of Imatinib Mesylate.

   Protocol Submission: 11/2004
   Study Start: 12/2004
   Final Report Submission: 06/2008

3. You have agreed to submit the complete study report (24 months follow-up) and data from the study, CA-180-006, a phase 2 multicenter study of dasatinib (BMS-354825) in subjects with Myeloid Blast Phase Chronic Myeloid Leukemia resistant to or intolerant of Imatinib Mesylate.

   Protocol Submission: 11/2004
   Study Start: 12/2004
   Final Report Submission: 06/2008

4. You have agreed to submit the complete study report (24 month follow-up) and data from the study, CA-180-013, a phase 2 multicenter study of dasatinib (BMS-354825) in subjects with Chronic Phase Philadelphia Chromosome Positive Chronic Myeloid Leukemia who have disease that is resistant to high dose Imatinib Mesylate or who are intolerant of Imatinib Mesylate.

   Protocol Submission: 11/2004
   Study Start: 02/2005
   Final Report Submission: 06/2008

5. You have agreed to submit the complete study report (24 month follow-up) and data from the study, CA-180-017, a randomized, open-label multicenter study of dasatinib (BMS-354825) versus Imatinib Mesylate (Gleevec, Glivec) 800 mg/d in subjects with Chronic Phase Philadelphia Chromosome Positive Chronic Myeloid Leukemia who have disease that is resistant to Imatinib Mesylate at a Dose of 400 - 600 mg/d.

   Protocol Submission: 11/2004
   Study Start: 02/2005
   Final Report Submission: 12/2008

6. You have agreed to submit the complete study report (24 month follow-up) and data from the study, CA-180-015, a phase 2 multicenter study of dasatinib (BMS-354825) in subjects with Lymphoid Blast Phase Chronic Myeloid Leukemia or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia resistant to high dose Imatinib Mesylate (Gleevec) or who are intolerant of Imatinib Mesylate.

   Protocol Submission: 11/2004
   Study Start: 01/2005
   Final Report Submission: 06/2008

The following previously agreed upon postmarketing commitment is a condition for accelerated approval of these supplements. Therefore, this commitment is now a Subpart H postmarketing study commitment.

7. You have agreed to submit the completed study report (24 month follow-up) and data from the study, CA-180-034, a randomized, two-by-two, open-label study of dasatinib (BMS-354825) in subjects with Chronic Phase Philadelphia Chromosome Positive Chronic Myeloid Leukemia resistant to or intolerant of Imatinib Mesylate.

   Protocol Submission: 04/2005
   Study Start: 07/2005
   Final Report Submission: 06/2009

Submit final study reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to these postmarketing study commitments must be clearly designated "**Subpart H Postmarketing Study Commitments**."

In addition, we note your following postmarketing study commitment, specified in your submission dated June 27, 2006, that is not a condition of the accelerated approval. This commitment is listed below:

8. You have agreed to submit the complete study report and data from the study, CA-180-051, a single-dose, pharmacokinetic study of BMS-354825 in subjects with hepatic impairment compared to healthy adult subjects.

   Protocol Submission: 05/2006
   Study Start: 10/2006
   Final Report Submission: 01/2009

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA.

In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

Promotional materials should be submitted, in duplicate, directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Milinda Vialpando, Regulatory Project Manager, at (301) 796-1444.

Sincerely,

{See appended electronic signature page}

Robert Justice, M.D.
Division Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Justice
11/8/2007 05:51:28 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-986/S001 & 002

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SPRYCEL safely and effectively. See full prescribing information for SPRYCEL.

SPRYCEL® (dasatinib) Tablet for Oral Use
Initial U.S. Approval: 2006

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2)	11/2007
Warnings and Precautions, Myelosuppression (5.1)	11/2007
Warnings and Precautions, Fluid Retention (5.3)	11/2007

----------INDICATIONS AND USAGE----------

SPRYCEL is a kinase inhibitor indicated for

- treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy including imatinib. (1, 14)
- treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy. (1, 14)

----------DOSAGE AND ADMINISTRATION----------

- Chronic phase CML: 100 mg once daily. (2)
- Accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL: 70 mg twice daily. (2)

Administered orally, with or without a meal. Tablets should not be crushed or cut. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 20 mg, 50 mg, 70 mg. (3, 16)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- *Myelosuppression* Severe thrombocytopenia, neutropenia, and anemia may occur and require dose interruption or reduction. Monitor complete blood counts regularly. (2.3, 5.1, 6.1)
- *Bleeding Related Events (mostly associated with severe thrombocytopenia)* CNS hemorrhages, including fatalities, have occurred. Severe gastrointestinal hemorrhage may require treatment interruptions and transfusions. Use SPRYCEL with caution in patients requiring medications that inhibit platelet function or anticoagulants. (5.2, 6.1)
- *Fluid Retention* SPRYCEL is associated with fluid retention, sometimes severe, including ascites, edema, and pleural and pericardial effusions. Manage with appropriate supportive care measures. (5.3, 6.1)
- *QT Prolongation* Use SPRYCEL with caution in patients who have or may develop prolongation of the QT interval. (5.4)
- Fetal harm may occur when administered to a pregnant woman. Women should be advised of the potential hazard to the fetus and to avoid becoming pregnant. (5.5)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥20%) included fluid retention events, diarrhea, headache, skin rash, nausea, hemorrhage, fatigue, and dyspnea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- *CYP3A4 Inhibitors*: May increase dasatinib drug levels and should be avoided. If coadministration cannot be avoided, monitor closely and consider reducing SPRYCEL dose. (2.1, 7.1)
- *CYP3A4 Inducers* May decrease dasatinib drug levels. If coadministration cannot be avoided, consider increasing SPRYCEL dose. (2.1, 7.2)
- *Antacids* May decrease dasatinib drug levels. Avoid simultaneous administration. If needed, administer the antacid at least 2 hours prior to or 2 hours after the dose of SPRYCEL. (7.2)
- *H_2 Antagonists/Proton Pump Inhibitors* May decrease dasatinib drug levels. Consider antacids in place of H_2 antagonists or proton pump inhibitors. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- *Hepatic Impairment* Use SPRYCEL with caution in patients with hepatic impairment. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 11/2007

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SPRYCEL® (dasatinib) is indicated for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy including imatinib. The effectiveness of SPRYCEL is based on hematologic and cytogenetic response rates *[see Clinical Studies (14)]*. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

SPRYCEL is also indicated for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

The recommended starting dosage of SPRYCEL (dasatinib) for chronic phase CML is 100 mg administered orally once daily (QD), either in the morning or in the evening. The recommended starting dosage of SPRYCEL for accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL is 140 mg/day administered orally in two divided doses (70 mg twice daily [BID]), one in the morning and one in the evening. Tablets should not be crushed or cut; they should be swallowed whole. SPRYCEL can be taken with or without a meal.

In clinical studies, treatment with SPRYCEL was continued until disease progression or until no longer tolerated by the patient. The effect of stopping treatment after the achievement of a complete cytogenetic response (CCyR) has not been investigated.

2.1 Dose Modification

Concomitant Strong CYP3A4 inducers: The use of concomitant strong CYP3A4 inducers may decrease dasatinib plasma concentrations and should be avoided (eg, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital). St. John's Wort may decrease dasatinib plasma concentrations unpredictably and should be avoided. If patients must be coadministered a strong CYP3A4 inducer, based on pharmacokinetic studies, a SPRYCEL dose increase should be considered. If the dose of SPRYCEL is

increased, the patient should be monitored carefully for toxicity *[see Drug Interactions (7.2)]*.

Concomitant Strong CYP3A4 inhibitors: CYP3A4 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) may increase dasatinib plasma concentrations. Grapefruit juice may also increase plasma concentrations of dasatinib and should be avoided.

Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. If SPRYCEL must be administered with a strong CYP3A4 inhibitor, a dose decrease to 20 mg daily should be considered. If 20 mg/day is not tolerated, either the strong CYP3A4 inhibitor must be discontinued, or SPRYCEL should be stopped until treatment with the inhibitor has ceased. When the strong inhibitor is discontinued, a washout period of approximately 1 week should be allowed before the SPRYCEL dose is increased. *[See Drug Interactions (7.1)]*.

2.2 Dose Escalation

In clinical studies of adult CML and Ph+ ALL patients, dose escalation to 140 mg once daily (chronic phase CML) or 100 mg twice daily (advanced phase CML and Ph+ ALL) was allowed in patients who did not achieve a hematologic or cytogenetic response at the recommended starting dosage.

2.3 Dose Adjustment for Adverse Reactions

Myelosuppression

In clinical studies, myelosuppression was managed by dose interruption, dose reduction, or discontinuation of study therapy. Hematopoietic growth factor has been used in patients with resistant myelosuppression. Guidelines for dose modifications are summarized in Table 1.

Table 1: Dose Adjustments for Neutropenia and Thrombocytopenia

Chronic Phase CML (starting dose 100 mg once daily)	ANC* $<0.5 \times 10^9$/L or Platelets $<50 \times 10^9$/L	1. Stop SPRYCEL until ANC $\geq 1.0 \times 10^9$/L and platelets $\geq 50 \times 10^9$/L. 2. Resume treatment with SPRYCEL at the original starting dose if recovery occurs in ≤7 days. 3. If platelets $<25 \times 10^9$/L or recurrence of ANC $<0.5 \times 10^9$/L for >7 days, repeat Step 1 and resume SPRYCEL at a reduced dose of 80 mg once daily (second episode) or discontinue (third episode).
Accelerated Phase CML, Blast Phase CML and Ph+ ALL (starting dose 70 mg twice daily)	ANC $<0.5 \times 10^9$/L or Platelets $<10 \times 10^9$/L	1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukemia, stop SPRYCEL until ANC $\geq 1.0 \times 10^9$/L and platelets $\geq 20 \times 10^9$/L and resume at the original starting dose. 3. If recurrence of cytopenia, repeat Step 1 and resume SPRYCEL at a reduced dose of 50 mg twice daily (second episode) or 40 mg twice daily (third episode). 4. If cytopenia is related to leukemia, consider dose escalation to 100 mg twice daily.

*ANC: absolute neutrophil count

Non-hematological adverse reactions

If a severe non-hematological adverse reaction develops with SPRYCEL use, treatment must be withheld until the event has resolved or improved. Thereafter, treatment can be resumed as appropriate at a reduced dose depending on the initial severity of the event.

3 DOSAGE FORMS AND STRENGTHS

SPRYCEL (dasatinib) Tablets are available as 20-mg, 50-mg, or 70-mg white to off-white, biconvex, film-coated tablets. *[See How Supplied (16.1)]*.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Treatment with SPRYCEL is associated with severe (NCI CTC Grade 3 or 4) thrombocytopenia, neutropenia, and anemia. Their occurrence is more frequent in patients with advanced phase CML or Ph+ ALL than in chronic phase CML. Complete blood counts should be performed weekly for the first 2 months and then monthly thereafter, or as clinically indicated. Myelosuppression was generally reversible and usually managed by withholding SPRYCEL temporarily or dose reduction *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)]*. In a Phase 3 dose-optimization study in patients with chronic phase CML, Grade 3 or 4 myelosuppression was reported less frequently in patients treated with 100 mg once daily than in patients treated with 70 mg twice daily *[see Table 6, Adverse Reactions (6.1)]*.

5.2 Bleeding Related Events

In addition to causing thrombocytopenia in human subjects, dasatinib caused platelet dysfunction *in vitro*. In all clinical studies, severe central nervous system (CNS) hemorrhages, including fatalities, occurred in <1% of patients receiving SPRYCEL. Severe gastrointestinal hemorrhage occurred in 4% of patients and generally required treatment interruptions and transfusions. Other cases of severe hemorrhage occurred in 2% of patients. Most bleeding events were associated with severe thrombocytopenia *[see Adverse Reactions (6.1)]*.

Patients were excluded from participation in SPRYCEL clinical studies if they took medications that inhibit platelet function or anticoagulants. In some trials, the use of anticoagulants, aspirin, and non-steroidal anti-inflammatory drugs (NSAIDs) was allowed concurrently with SPRYCEL if the platelet count was >50,000. Caution should be exercised if patients are required to take medications that inhibit platelet function or anticoagulants.

5.3 Fluid Retention

SPRYCEL is associated with fluid retention. In all clinical studies, severe fluid retention was reported in 8% of patients, including pleural and pericardial effusion reported in 5% and 1% of patients, respectively. Severe ascites and generalized edema were each reported in <1% of patients. Severe pulmonary edema was reported in 1% of patients *[see Adverse Reactions (6.1)]*. Patients who develop symptoms suggestive of pleural

effusion such as dyspnea or dry cough should be evaluated by chest X-ray. Severe pleural effusion may require thoracentesis and oxygen therapy. Fluid retention events were typically managed by supportive care measures that include diuretics or short courses of steroids.

In the Phase 3 dose-optimization study in patients with chronic phase CML, fluid retention events were reported less frequently in patients treated with 100 mg once daily than in patients treated with 70 mg twice daily *[see Table 4, Adverse Reactions (6.1)]*.

5.4 QT Prolongation

In vitro data suggest that dasatinib has the potential to prolong cardiac ventricular repolarization (QT interval). In single-arm clinical studies in patients with leukemia treated with SPRYCEL, the mean QTc interval changes from baseline using Fridericia's method (QTcF) were 3–6 msec; the upper 95% confidence intervals for all mean changes from baseline were <8 msec. Nine patients had QTc prolongation reported as an adverse event. Three patients (<1%) experienced a QTcF >500 msec.

SPRYCEL should be administered with caution to patients who have or may develop prolongation of QTc. These include patients with hypokalemia or hypomagnesemia, patients with congenital long QT syndrome, patients taking anti-arrhythmic medicines or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy. Hypokalemia or hypomagnesemia should be corrected prior to SPRYCEL administration.

5.5 Pregnancy

Pregnancy Category D: SPRYCEL may cause fetal harm when administered to a pregnant woman. In nonclinical studies, at plasma concentrations below those observed in humans receiving therapeutic doses of dasatinib, fetal toxicity was observed in rats and rabbits. Fetal death was observed in rats. In both rats and rabbits, the lowest doses of dasatinib tested (rat: 2.5 mg/kg/day [15 mg/m^2/day] and rabbit: 0.5 mg/kg/day [6 mg/m^2/day]) resulted in embryo-fetal toxicities. These doses produced maternal AUCs of 105 ng•hr/mL (0.3-fold the human AUC in females at a dose of 70 mg twice daily) and 44 ng•hr/mL (0.1-fold the human AUC) in rats and rabbits, respectively. Embryo-fetal toxicities included skeletal malformations at multiple sites (scapula, humerus, femur, radius, ribs, clavicle), reduced ossification (sternum; thoracic, lumbar, and sacral vertebrae; forepaw phalanges; pelvis; and hyoid body), edema, and microhepatia.

Women should be advised of the potential hazard to the fetus and to avoid becoming pregnant. If SPRYCEL is used during pregnancy, or if the patient becomes pregnant while taking SPRYCEL, the patient should be apprised of the potential hazard to the fetus.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling.

- Myelosuppression *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)]*.
- Bleeding related events *[see Warnings and Precautions (5.2)]*.
- Fluid retention *[see Warnings and Precautions (5.3)]*.
- QT prolongation *[see Warnings and Precautions (5.4)]*.

6.1 Clinical Studies Experience

The data described below reflect exposure to SPRYCEL in 2182 patients with leukemia in clinical studies (starting dosage 100 mg once daily, 140 mg once daily, 50 mg twice daily, or 70 mg twice daily). The median duration of therapy was 11 months (range 0.03–26 months).

The majority of SPRYCEL-treated patients experienced adverse reactions at some time. Drug was discontinued for adverse reactions in 9% of patients in chronic phase CML, 10% in accelerated phase CML, 15% in myeloid blast phase CML, and 8% in lymphoid blast phase CML or Ph+ ALL. In a Phase 3 dose-optimization study in patients with chronic phase CML, the rate of discontinuation for adverse reaction was lower in patients treated with 100 mg once daily than in patients treated with 70 mg twice daily (4% and 12%, respectively).

The most frequently reported adverse reactions (reported in ≥20% of patients) included fluid retention events, diarrhea, headache, skin rash, nausea, hemorrhage, fatigue, and dyspnea.

The most frequently reported serious adverse reactions included pleural effusion (9%), pyrexia (3%), pneumonia (3%), infection (2%), febrile neutropenia (4%), gastrointestinal

bleeding (4%), dyspnea (3%), sepsis (1%), diarrhea (2%), congestive heart failure (2%), and pericardial effusion (1%).

All adverse reactions (excluding laboratory abnormalities) that were reported in at least 10% of the patients in SPRYCEL clinical studies are shown in Table 2.

Table 2: Adverse Reactions Reported in ≥10% of All Patients (All Grades) in Clinical Studies

	All Patients (n=2182)		Chronic Phase[a] (n=1150)	Accelerated Phase (n=502)	Myeloid Blast Phase (n=280)	Lymphoid Blast Phase and Ph+ ALL (n=250)
	All Grades	Grades 3/4	Grades 3/4	Grades 3/4	Grades 3/4	Grades 3/4
Preferred Term	**Percent (%) of Patients**					
Fluid Retention	37	8	6	7	13	7
Superficial localized edema	20	<1	<1	1	1	<1
Pleural effusion	22	5	4	5	10	6
Other fluid retention	10	3	3	3	6	2
Generalized edema	3	<1	<1	1	<1	1
Congestive heart failure/cardiac dysfunction[b]	2	1	2	<1	2	1
Pericardial effusion	3	1	1	1	2	0
Pulmonary edema	2	1	1	1	1	1
Ascites	<1	<1	0	0	1	<1
Pulmonary hypertension	1	<1	<1	0	1	1
Diarrhea	31	3	3	4	5	4
Headache	24	1	1	1	1	2
Skin Rash[c]	22	1	1	1	1	1
Nausea	22	1	1	1	2	2
Hemorrhage	21	6	2	11	12	8
Gastrointestinal bleeding	7	4	1	8	9	5
CNS bleeding	1	<1	0	<1	<1	2
Fatigue	21	2	2	3	1	2
Dyspnea	20	4	5	4	5	2
Musculoskeletal Pain	14	1	2	1	1	<1
Pyrexia	13	1	1	2	3	1
Vomiting	13	1	1	1	1	2

Table 2: Adverse Reactions Reported in ≥10% of All Patients (All Grades) in Clinical Studies

	All Patients (n=2182)		Chronic Phase[a] (n=1150)	Accelerated Phase (n=502)	Myeloid Blast Phase (n=280)	Lymphoid Blast Phase and Ph+ ALL (n=250)
	All Grades	Grades 3/4	Grades 3/4	Grades 3/4	Grades 3/4	Grades 3/4
Preferred Term	**Percent (%) of Patients**					
Abdominal Pain	10	1	1	<1	1	2

[a] The chronic phase data include patients prescribed any dose of SPRYCEL. For selected adverse reactions in patients with chronic phase CML receiving the recommended 100 mg once daily starting dose, see Table 4.

[b] Includes left ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and ventricular failure.

[c] Includes erythema, erythema multiforme, exfoliative rash, generalized erythema, heat rash, milia, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, skin exfoliation, skin irritation, systemic lupus erythematosus rash, urticaria vesiculosa, and rash vesicular.

In a Phase 2 randomized study of chronic phase CML, 101 patients received SPRYCEL (starting dosage 70 mg twice daily) and 49 patients received imatinib (starting dosage 800 mg daily [400 mg twice daily]). Crossover to the alternate therapy was permitted in this study. The median duration of therapy prior to crossover was longer for SPRYCEL (19 months) than for imatinib (3 months). Selected adverse reactions are presented in Table 3.

Table 3: Selected Adverse Reactions in Phase 2 Randomized Study (Chronic Phase CML)

	SPRYCEL[a] (n=101)		Imatinib[a] (n=49)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Preferred Term	Percent (%) of Patients			
Diarrhea	37	2	29	2
Fluid Retention	36	7	43	0
Pleural effusion	23	5	0	0
Superficial localized edema	17	1	41	0
Generalized edema	2	0	4	0
Congestive heart failure/cardiac dysfunction[b]	2	1	0	0
Pericardial effusion	1	0	0	0
Pulmonary edema	3	2	0	0
Pulmonary hypertension	1	0	0	0
Nausea	24	0	33	0
Hemorrhage	18	1	8	0
Gastrointestinal bleeding	3	1	0	0
Vomiting	10	0	24	0

[a] Starting dosage: SPRYCEL 70 mg twice daily; imatinib 800 mg daily (400 mg twice daily).

[b] Includes left ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and ventricular failure.

In the Phase 3 dose-optimization study in patients with chronic phase CML, the median duration of therapy was approximately 12 months (range <1–20 months). Selected adverse reactions are shown by dose regimen in Table 4.

Table 4: Selected Adverse Reactions Reported in Phase 3 Dose-Optimization Study (Chronic Phase CML)

	100 mg QD (n=165)		140 mg QD[a] (n=163)		50 mg BID[a] (n=167)		70 mg BID[a] (n=167)	
	All Grades	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Preferred Term	**Percent (%) of Patients**							
Diarrhea	23	1	26	3	26	3	25	4
Fluid Retention	24	2	33	4	27	4	32	5
Superficial localized edema	14	0	14	1	14	0	16	0
Pleural effusion	10	2	20	2	16	3	18	2
Generalized edema	2	0	3	0	0	0	1	0
Congestive heart failure/cardiac dysfunction[b]	0	0	2	1	1	1	4	2
Pericardial effusion	1	1	4	1	2	1	2	1
Pulmonary edema	0	0	0	0	1	0	2	1
Pulmonary hypertension	0	0	0	0	0	0	1	1
Hemorrhage	10	1	12	1	9	2	14	2
Gastrointestinal bleeding	1	1	2	0	4	2	4	2

[a] Not a recommended starting dosage of SPRYCEL for chronic phase CML.

[b] Includes left ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and ventricular failure.

Laboratory Abnormalities

Myelosuppression was commonly reported in all patient populations. The frequency of Grade 3 or 4 neutropenia, thrombocytopenia, and anemia was higher in patients with advanced phase CML or Ph+ ALL than in chronic phase CML (Table 5). Myelosuppression was reported in patients with normal baseline laboratory values as well as in patients with pre-existing laboratory abnormalities.

In patients who experienced severe myelosuppression, recovery generally occurred following dose interruption or reduction; permanent discontinuation of treatment occurred in 1% of patients *[see Warnings and Precautions (5.1)]*.

Grade 3 or 4 elevations of transaminase or bilirubin and Grade 3 or 4 hypocalcemia and hypophosphatemia were reported in patients with all phases of CML but were reported with an increased frequency in patients with myeloid or lymphoid blast phase CML and Ph+ ALL. Elevations in transaminase or bilirubin were usually managed with dose

reduction or interruption. Patients developing Grade 3 or 4 hypocalcemia during the course of SPRYCEL therapy often had recovery with oral calcium supplementation.

In the Phase 2 randomized study, the frequency of Grade 3 or 4 neutropenia, thrombocytopenia, and anemia was 63%, 56%, and 19%, respectively, in the SPRYCEL group and 39%, 14%, and 8%, respectively, in the imatinib group. The frequency of Grade 3 or 4 hypocalcemia was 4% in the SPRYCEL group and 0% in the imatinib group. Laboratory abnormalities reported in the Phase 3 dose-optimization study in patients with chronic phase CML are shown in Table 6.

Table 5: CTC Grades 3/4 Laboratory Abnormalities in Clinical Studies

	Chronic Phase[a] (n=1150)	Accelerated Phase (n=502)	Myeloid Blast Phase (n=280)	Lymphoid Blast Phase and Ph+ ALL (n=250)
	Percent (%) of Patients			
Hematology Parameters				
Neutropenia	46	68	80	78
Thrombocytopenia	41	71	81	78
Anemia	18	55	75	45
Biochemistry Parameters				
Hypophosphatemia	10	12	19	20
Hypocalcemia	2	7	16	11
Elevated SGPT (ALT)	1	3	6	7
Elevated SGOT (AST)	1	1	4	5
Elevated Bilirubin	1	1	4	5
Elevated Creatinine	1	2	3	1

a The chronic phase data include patients prescribed any dose of SPRYCEL. For laboratory abnormalities in patients with chronic phase CML receiving the recommended 100 mg once daily starting dose, see Table 6.

CTC grades: neutropenia (Grade 3 ≥0.5–1.0 × 10^9/L, Grade 4 <0.5 × 10^9/L); thrombocytopenia (Grade 3 ≥10–50 × 10^9/L, Grade 4 <10 × 10^9/L); anemia (hemoglobin ≥65–80 g/L, Grade 4 <65 g/L); elevated creatinine (Grade 3 >3–6 × upper limit of normal range (ULN), Grade 4 >6 × ULN); elevated bilirubin (Grade 3 >3–10 × ULN, Grade 4 >10 × ULN); elevated SGOT or SGPT (Grade 3 >5–20 × ULN, Grade 4 >20 × ULN); hypocalcemia (Grade 3 <7.0–6.0 mg/dL, Grade 4 <6.0 mg/dL); hypophosphatemia (Grade 3 <2.0–1.0 mg/dL, Grade 4 <1.0 mg/dL).

Table 6: CTC Grades 3/4 Laboratory Abnormalities in Phase 3 Dose-Optimization Study (Chronic Phase CML)

	100 mg QD (n=165)	140 mg QD[a] (n=163)	50 mg BID[a] (n=167)	70 mg BID[a] (n=167)
	Percent (%) of Patients			
Hematology Parameters				
Neutropenia	34	43	46	43
Thrombocytopenia	22	40	34	38
Anemia	10	19	18	17
Biochemistry Parameters				
Hypophosphatemia	8	6	7	7
Hypocalcemia	2	3	1	2
Elevated SGPT (ALT)	0	1	1	1
Elevated SGOT (AST)	1	1	0	0
Elevated Bilirubin	1	2	0	1
Elevated Creatinine	0	1	0	1

[a] Not a recommended starting dosage of SPRYCEL for chronic phase CML.

CTC grades: neutropenia (Grade 3 ≥0.5–1.0 × 10^9/L, Grade 4 <0.5 × 10^9/L); thrombocytopenia (Grade 3 ≥10–50 ×10^9/L, Grade 4 <10 × 10^9/L); anemia (hemoglobin ≥65–80 g/L, Grade 4 <65 g/L); elevated creatinine (Grade 3 >3–6 × upper limit of normal range (ULN), Grade 4 >6 × ULN); elevated bilirubin (Grade 3 >3–10 × ULN, Grade 4 >10 × ULN); elevated SGOT or SGPT (Grade 3 >5–20 × ULN, Grade 4 >20 × ULN); hypocalcemia (Grade 3 <7.0–6.0 mg/dL, Grade 4 <6.0 mg/dL); hypophosphatemia (Grade 3 <2.0–1.0 mg/dL, Grade 4 <1.0 mg/dL).

Additional Data From Clinical Trials

The following adverse reactions were reported in patients in the SPRYCEL clinical studies at a frequency of <10% (1%–<10%, 0.1%–<1%, or <0.1%). These events are included on the basis of clinical relevance.

Gastrointestinal Disorders: *1%–<10%* – mucosal inflammation (including mucositis/stomatitis), dyspepsia, abdominal distension, constipation, gastritis, oral soft tissue disorder, colitis (including neutropenic colitis); *0.1%–<1%* – dysphagia, anal fissure, upper gastrointestinal ulcer, pancreatitis; *<0.1%* – esophagitis.

General Disorders and Administration Site Conditions: *1%–<10%* – asthenia, pain, chest pain, chills; *0.1%–<1%* – malaise; *<0.1%* – temperature intolerance.

Skin and Subcutaneous Tissue Disorders: *1%–<10%* – pruritus, acne, alopecia, dry skin, hyperhidrosis, urticaria, dermatitis (including eczema); *0.1%–<1%* – skin ulcer, bullous conditions, pigmentation disorder, nail disorder, photosensitivity, acute febrile neutrophilic dermatosis, panniculitis; *<0.1%* – palmar-plantar erythrodysesthesia syndrome.

Respiratory, Thoracic, and Mediastinal Disorders: *1%–<10%* – cough, lung infiltration, pneumonitis; *0.1%–<1%* – asthma, bronchospasm; *<0.1%* – acute respiratory distress syndrome.

Nervous System Disorders: *1%–<10%* – neuropathy (including peripheral neuropathy), dizziness, dysgeusia, somnolence; *0.1%–<1%* – tremor, syncope, amnesia; *<0.1%* – convulsion, cerebrovascular accident, transient ischemic attack.

Blood and Lymphatic System Disorders: *1%–<10%* – febrile neutropenia, pancytopenia; *<0.1%* – aplasia pure red cell.

Musculoskeletal and Connective Tissue Disorders: *1%–<10%* – arthralgia, myalgia, muscle inflammation, muscular weakness; *0.1%–<1%* – musculoskeletal stiffness, rhabdomyolysis; *<0.1%* – tendonitis.

Investigations: *1%–<10%* – weight decreased, weight increased; *0.1%–<1%* – blood creatine phosphokinase increased.

Infections and Infestations: *1%–<10%* – infections (including bacterial, viral, fungal, non-specified), pneumonia (including bacterial, viral, and fungal), upper respiratory tract infection/inflammation, herpes virus infection, enterocolitis infection; *0.1%–<1%* – sepsis (including fatal outcomes).

Metabolism and Nutrition Disorders: *1%–<10%* – anorexia, appetite disturbances; *0.1%–<1%* – hyperuricemia.

Cardiac Disorders: *1%–<10%* – arrhythmia (including tachycardia), palpitations; *0.1%–<1%* – angina pectoris, cardiomegaly, pericarditis, ventricular arrhythmia (including ventricular tachycardia), myocardial infarction; *<0.1%* – myocarditis, acute coronary syndrome.

Eye Disorders: *1%–<10%* – visual disorder, dry eye; *0.1% –<1%* – conjunctivitis.

Vascular Disorders: *1%–<10%* – flushing, hypertension; *0.1%–<1%* – hypotension, thrombophlebitis; *<0.1%* – livedo reticularis.

Psychiatric Disorders: *1%–<10%* – insomnia, depression; *0.1%–<1%* – anxiety, affect lability, confusional state, libido decreased.

Reproductive System and Breast Disorders: *0.1%–<1%* – gynecomastia, menstruation irregular.

Injury, Poisoning, and Procedural Complications: *1%–<10%* – contusion.

Ear and Labyrinth Disorders: *0.1%–<1%* – tinnitus, vertigo.

Hepatobiliary Disorders: *0.1%–<1%* – cholecystitis, hepatitis; *<0.1%* – cholestasis.

Renal and Urinary Disorders: *0.1%–<1%* – renal failure, urinary frequency, proteinuria.

Neoplasms Benign, Malignant, and Unspecified: *0.1%–<1%* – tumor lysis syndrome.

Immune System Disorders: *0.1%–<1%* – hypersensitivity (including erythema nodosum).

7 DRUG INTERACTIONS

7.1 Drugs That May Increase Dasatinib Plasma Concentrations

CYP3A4 Inhibitors: Dasatinib is a CYP3A4 substrate. In a study of 18 patients with solid tumors, 20-mg SPRYCEL once daily coadministered with 200 mg of ketoconazole twice daily increased the dasatinib C_{max} and AUC by four- and five-fold, respectively. Concomitant use of SPRYCEL and drugs that inhibit CYP3A4 may increase exposure to dasatinib and should be avoided. In patients receiving treatment with SPRYCEL, close monitoring for toxicity and a SPRYCEL dose reduction should be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided *[see Dosage and Administration (2.1)]*.

7.2 Drugs That May Decrease Dasatinib Plasma Concentrations

CYP3A4 Inducers: When a single morning dose of SPRYCEL was administered following 8 days of continuous evening administration of 600 mg of rifampin, a potent CYP3A4 inducer, the mean C_{max} and AUC of dasatinib were decreased by 81% and 82%, respectively. Alternative agents with less enzyme induction potential should be considered. If SPRYCEL must be administered with a CYP3A4 inducer, a dose increase in SPRYCEL should be considered *[see Dosage and Administration (2.1)]*.

Antacids: Nonclinical data demonstrate that the solubility of dasatinib is pH dependent. In a study of 24 healthy subjects, administration of 30 mL of aluminum

hydroxide/magnesium hydroxide 2 hours prior to a single 50-mg dose of SPRYCEL was associated with no relevant change in dasatinib AUC; however, the dasatinib C_{max} increased 26%. When 30 mL of aluminum hydroxide/magnesium hydroxide was administered to the same subjects concomitantly with a 50-mg dose of SPRYCEL, a 55% reduction in dasatinib AUC and a 58% reduction in C_{max} were observed. Simultaneous administration of SPRYCEL with antacids should be avoided. If antacid therapy is needed, the antacid dose should be administered at least 2 hours prior to or 2 hours after the dose of SPRYCEL.

H_2 Antagonists/Proton Pump Inhibitors: Long-term suppression of gastric acid secretion by H_2 antagonists or proton pump inhibitors (eg, famotidine and omeprazole) is likely to reduce dasatinib exposure. In a study of 24 healthy subjects, administration of a single 50-mg dose of SPRYCEL 10 hours following famotidine reduced the AUC and C_{max} of dasatinib by 61% and 63%, respectively. The concomitant use of H_2 antagonists or proton pump inhibitors with SPRYCEL is not recommended. The use of antacids should be considered in place of H_2 antagonists or proton pump inhibitors in patients receiving SPRYCEL therapy.

7.3 Drugs That May Have Their Plasma Concentration Altered By Dasatinib

CYP3A4 Substrates: Single-dose data from a study of 54 healthy subjects indicate that the mean C_{max} and AUC of simvastatin, a CYP3A4 substrate, were increased by 37% and 20%, respectively, when simvastatin was administered in combination with a single 100-mg dose of SPRYCEL. Therefore, CYP3A4 substrates known to have a narrow therapeutic index such as alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, or ergot alkaloids (ergotamine, dihydroergotamine) should be administered with caution in patients receiving SPRYCEL.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.5)]*.

8.3 Nursing Mothers

It is unknown whether SPRYCEL is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from SPRYCEL, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and efficacy of SPRYCEL in patients <18 years of age have not been established.

8.5 Geriatric Use

Of the 2182 patients in clinical studies of SPRYCEL, 547 (25%) were 65 years of age and over, and 105 (5%) were 75 years of age and over. While the safety profile of SPRYCEL in the geriatric population was similar to that in the younger population, patients aged 65 years and older are more likely to experience fluid retention events and should be monitored closely. No differences in efficacy were observed between older and younger patients. However, in the two randomized studies in patients with chronic phase CML, the rates of major cytogenetic response (MCyR) were lower among patients aged 65 years and over.

8.6 Hepatic Impairment

There are currently no clinical studies with SPRYCEL in patients with impaired liver function (clinical studies excluded patients with ALT or AST >2.5 times the upper limit of the normal range or total bilirubin >2 times the upper limit of the normal range). Metabolism of dasatinib is mainly hepatic. Caution is recommended in patients with hepatic impairment.

8.7 Renal Impairment

There are currently no clinical studies with SPRYCEL in patients with impaired renal function. Less than 4% of dasatinib and its metabolites are excreted via the kidney.

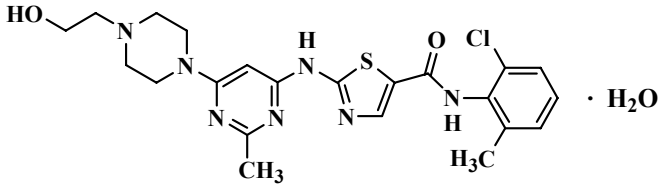
10 OVERDOSAGE

Experience with overdose of SPRYCEL in clinical studies is limited to isolated cases. The highest reported dosage ingested was 280 mg per day for 1 week in two patients and both developed severe myelosuppression and bleeding. Since SPRYCEL is associated with severe myelosuppression *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*, patients who ingested more than the recommended dosage should be closely monitored for myelosuppression and appropriate supportive treatment given.

Acute overdose in animals was associated with cardiotoxicity. Evidence of cardiotoxicity included ventricular necrosis and valvular/ventricular/atrial hemorrhage at single doses ≥100 mg/kg (600 mg/m^2) in rodents. There was a tendency for increased systolic and diastolic blood pressure in monkeys at single doses ≥10 mg/kg (120 mg/m^2).

11 DESCRIPTION

SPRYCEL (dasatinib) is an inhibitor of multiple tyrosine kinases. The chemical name for dasatinib is N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, monohydrate. The molecular formula is $C_{22}H_{26}ClN_7O_2S \bullet H_2O$, which corresponds to a formula weight of 506.02 (monohydrate). The anhydrous free base has a molecular weight of 488.01. Dasatinib has the following chemical structure:



Dasatinib is a white to off-white powder and has a melting point of 280°–286° C. The drug substance is insoluble in water and slightly soluble in ethanol and methanol. SPRYCEL tablets are white to off-white, biconvex, film-coated tablets containing dasatinib, with the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The tablet coating consists of hypromellose, titanium dioxide, and polyethylene glycol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dasatinib, at nanomolar concentrations, inhibits the following kinases: BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EPHA2, and PDGFRβ. Based on modeling studies, dasatinib is predicted to bind to multiple conformations of the ABL kinase.

In vitro, dasatinib was active in leukemic cell lines representing variants of imatinib mesylate sensitive and resistant disease. Dasatinib inhibited the growth of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) cell lines overexpressing BCR-ABL. Under the conditions of the assays, dasatinib was able to overcome imatinib resistance resulting from BCR-ABL kinase domain mutations, activation of alternate signaling pathways involving the SRC family kinases (LYN, HCK), and multi-drug resistance gene overexpression.

12.3 Pharmacokinetics

Absorption

Maximum plasma concentrations (C_{max}) of dasatinib are observed between 0.5 and 6 hours (T_{max}) following oral administration. Dasatinib exhibits dose proportional increases in AUC and linear elimination characteristics over the dose range of 15 mg to 240 mg/day. The overall mean terminal half-life of dasatinib is 3–5 hours.

Data from a study of 54 healthy subjects administered a single, 100-mg dose of dasatinib 30 minutes following consumption of a high-fat meal resulted in a 14% increase in the mean AUC of dasatinib. The observed food effects were not clinically relevant.

Distribution

In patients, dasatinib has an apparent volume of distribution of 2505 L, suggesting that the drug is extensively distributed in the extravascular space. Binding of dasatinib and its active metabolite to human plasma proteins *in vitro* was approximately 96% and 93%, respectively, with no concentration dependence over the range of 100–500 ng/mL.

Metabolism

Dasatinib is extensively metabolized in humans, primarily by the cytochrome P450 enzyme 3A4. CYP3A4 was the primary enzyme responsible for the formation of the active metabolite. Flavin-containing monooxygenase 3 (FMO-3) and uridine diphosphate-glucuronosyltransferase (UGT) enzymes are also involved in the formation of dasatinib metabolites. In human liver microsomes, dasatinib was a weak time-dependent inhibitor of CYP3A4.

The exposure of the active metabolite, which is equipotent to dasatinib, represents approximately 5% of the dasatinib AUC. This indicates that the active metabolite of dasatinib is unlikely to play a major role in the observed pharmacology of the drug. Dasatinib also had several other inactive oxidative metabolites.

Dasatinib is a time-dependent inhibitor of CYP3A4. At clinically relevant concentrations, dasatinib does not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, or 2E1. Dasatinib is not an inducer of human CYP enzymes.

Elimination

Elimination is primarily via the feces. Following a single oral dose of [^{14}C]-labeled dasatinib, approximately 4% and 85% of the administered radioactivity was recovered in the urine and feces, respectively, within 10 days. Unchanged dasatinib accounted for 0.1% and 19% of the administered dose in urine and feces, respectively, with the remainder of the dose being metabolites.

Effects of Age and Gender

Pharmacokinetic analyses of demographic data indicate that there are no clinically relevant effects of age and gender on the pharmacokinetics of dasatinib.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies were not performed with dasatinib.

Dasatinib was clastogenic when tested *in vitro* in Chinese hamster ovary cells, with and without metabolic activation. Dasatinib was not mutagenic when tested in an *in vitro*

bacterial cell assay (Ames test) and was not genotoxic in an *in vivo* rat micronucleus study.

The effects of dasatinib on male and female fertility have not been studied. However, results of repeat-dose toxicity studies in multiple species indicate the potential for dasatinib to impair reproductive function and fertility. Effects evident in male animals included reduced size and secretion of seminal vesicles, and immature prostate, seminal vesicle, and testis. The administration of dasatinib resulted in uterine inflammation and mineralization in monkeys, and cystic ovaries and ovarian hypertrophy in rodents.

14 CLINICAL STUDIES

Phase 2 Single-Arm Studies

Four Phase 2, single-arm, multicenter studies were conducted to determine the efficacy and safety of SPRYCEL in patients with CML or Ph+ ALL resistant to or intolerant of treatment with imatinib. Resistance to imatinib included failure to achieve a complete hematologic response (within 3–6 months) or major cytogenetic response (by month 12) or progression of disease after a previous cytogenetic or hematologic response. Imatinib intolerance included inability to tolerate 400 mg or more of imatinib per day or discontinuation of imatinib because of toxicity. The chronic phase CML study enrolled 186 patients, the accelerated phase CML study 107 patients, the myeloid blast phase study 74 patients, and the lymphoid blast phase CML/Ph+ ALL study 78 patients. The studies are ongoing. The results are based on a minimum of 6 months follow-up after the start of SPRYCEL therapy. Across all studies, 49% of patients were women, 89% were white, 10% were black or Asian, 23% were over the age of 65 years, and 3% were over the age of 75 years. Most patients had long disease histories with extensive prior treatment, including imatinib, cytotoxic chemotherapy, interferon, and stem cell transplant (Table 7). The maximum imatinib dose had been 400–600 mg/day in about one-half of the patients and >600 mg/day in the other half.

Table 7: Disease History Characteristics, Phase 2 Single-Arm Studies

	Chronic (n=186)	Accelerated (n=107)	Myeloid Blast (n=74)	Lymphoid Blast (n=42)	Ph+ ALL (n=36)
Median time since diagnosis in months (range)	64 (4–251)	91 (4–355)	49 (3–216)	28 (2–186)	20 (3–97)
Imatinib					
Resistant	68%	93%	92%	88%	94%
Intolerant	32%	7%	8%	12%	6%
Imatinib					
>3 years	54%	68%	47%	24%	3%
>1 year	80%	92%	85%	52%	56%
Cytotoxic chemotherapy	42%	67%	66%	79%	92%
Interferon	70%	75%	55%	48%	8%
Stem cell transplant	9%	18%	12%	33%	42%

All patients were treated with SPRYCEL 70 mg twice daily on a continuous basis. The median durations of treatment are shown in Table 8.

Table 8: Duration of Treatment with SPRYCEL, Phase 2 Single-Arm Studies

	Chronic (n=186)	Accelerated (n=107)	Myeloid Blast (n=74)	Lymphoid Blast (n=42)	Ph+ ALL (n=36)
Median duration of therapy in months (range)	**5.6** (0.03–8.3)	**5.5** (0.2–10.1)	**3.5** (0.03–9.2)	**2.8** (0.1–6.4)	**3.2** (0.2–8.1)

The primary efficacy endpoint in chronic phase CML was major cytogenetic response (MCyR), defined as elimination (complete cytogenetic response, CCyR) or substantial diminution (by at least 65%, partial cytogenetic response) of Ph+ hematopoietic cells. The primary endpoint in accelerated phase, myeloid blast phase, and lymphoid blast phase CML, and Ph+ ALL was major hematologic response (MaHR), defined as either a complete hematologic response (CHR) or no evidence of leukemia (NEL) (defined in Table 9).

SPRYCEL treatment resulted in cytogenetic and hematologic responses in patients with all phases of CML and with Ph+ ALL. The response rates for the single-arm studies are reported in Table 9. In chronic phase CML patients, the MCyR rate was 45% with a complete response (0% Ph+ cells) rate of 33%. The MaHR rate was 59% in accelerated

phase patients, 32% in myeloid phase patients, 31% in lymphoid blast phase patients, and 42% in Ph+ ALL patients.

Most cytogenetic responses occurred after 12 weeks of treatment, when the first cytogenetic analyses were performed. Hematologic and cytogenetic responses were stable during the 6-month follow-up of patients with chronic phase, accelerated phase, and myeloid blast phase CML. The median durations of MaHR were 3.7 months in lymphoid blast CML and 4.8 months in Ph+ ALL.

There were no age- or gender-related response differences.

Table 9: Efficacy of SPRYCEL in Phase 2 Single-Arm Clinical Studies[a]

	Chronic (n=186)	Accelerated (n=107)	Myeloid Blast (n=74)	Lymphoid Blast (n=42)	Ph+ ALL (n=36)
Hematologic Response Rate[b] (%)					
MaHR (95% CI)	n/a	**59 (49–68)**	**32 (22–44)**	**31 (18–47)**	**42 (26–59)**
CHR (95% CI)	**90 (85–94)**	33 (24–42)	24 (15–36)	26 (14–42)	31 (16–48)
NEL (95% CI)	n/a	26 (18–36)	8 (3–17)	5 (0.6–16)	11 (3.1–26)
Cytogenetic Response[c] (%)					
MCyR (95% CI)	**45 (37–52)**	31 (22–41)	30 (20–42)	50 (34–66)	58 (41–74)
CCyR (95% CI)	33 (26–40)	21 (14–30)	27 (17–39)	43 (28–59)	58 (41–74)

[a] Numbers in bold font are the results of primary endpoints.

[b] Hematologic response criteria (all responses confirmed after 4 weeks): Major hematologic response: (MaHR) = complete hematologic response (CHR) + no evidence of leukemia (NEL).

CHR (chronic CML): WBC ≤ institutional ULN, platelets <450,000/mm^3, no blasts or promyelocytes in peripheral blood, <5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood <20%, and no extramedullary involvement.

CHR (advanced CML/Ph+ ALL): WBC ≤ institutional ULN, ANC ≥1000/mm^3, platelets ≥100,000/mm^3, no blasts or promyelocytes in peripheral blood, bone marrow blasts ≤5%, <5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood <20%, and no extramedullary involvement.

NEL: same criteria as for CHR but ANC ≥500/mm^3 and <1000/mm^3, or platelets ≥20,000/mm^3 and ≤100,000/mm^3.

[c] Cytogenetic response criteria: complete (0% Ph+ metaphases) or partial (>0%–35%). MCyR (0%–35%) combines both complete and partial responses.

n/a = not applicable.

Randomized Studies

Phase 2 randomized study of SPRYCEL 70 mg twice daily or imatinib 800 mg daily (400 mg twice daily). A randomized, open-label study was conducted in patients with chronic phase CML whose disease was resistant to prior imatinib therapy at doses of 400

or 600 mg. The primary endpoint was MCyR at 12 weeks. One hundred fifty patients were randomized in a 2:1 ratio to either SPRYCEL 70 mg twice daily or imatinib 800 mg daily (400 mg twice daily). Crossover to the alternate therapy was permitted in the event of disease progression or intolerable toxicity. Median follow-up was 15 months. Median duration of treatment prior to crossover was 14 months for SPRYCEL and 3 months for imatinib.

Prior to crossover, 93% of the SPRYCEL-treated patients and 82% of the imatinib-treated patients achieved a CHR. At 12 weeks, MCyR was achieved in 36% of the SPRYCEL-treated patients (CCyR in 22%) and 29% of the imatinib-treated patients (CCyR in 8%). With longer treatment and follow-up, MCyR was achieved in 52% of the SPRYCEL-treated patients (CCyR in 40%) and 33% of the imatinib-treated patients (CCyR in 16%) prior to crossover. Since the median follow-up was 15 months, there were too few progressions to reliably estimate the duration of MCyR.

Phase 3 dose-optimization study in chronic phase CML: A randomized, open-label study was conducted in patients with chronic phase CML, whose disease was resistant to or who were intolerant to imatinib, to evaluate the efficacy of SPRYCEL administered once daily compared with SPRYCEL administered twice daily. Patients with significant cardiac diseases including myocardial infarction within 6 months, congestive heart failure within 3 months, significant arrhythmias, or QTc prolongation were excluded from the study. The primary endpoint was MCyR in patients with imatinib-resistant chronic phase CML. The main secondary endpoint was MCyR by total daily dose level in the same population. A total of 670 patients, of whom 498 had imatinib resistant disease, were randomized to the SPRYCEL 100 mg once daily, 140 mg once daily, 50 mg twice daily, or 70 mg twice daily group. Minimum follow-up was 6 months and median duration of treatment was approximately 8 months.

Response rates are presented in Table 10. Efficacy was achieved across all SPRYCEL treatment groups with the once daily schedule demonstrating comparable efficacy (non-inferiority) to the twice daily schedule on the primary efficacy endpoint (difference in MCyR 2.8%; 95% confidence interval [-6.0%–11.6%]). The main secondary endpoint of the study also showed comparable efficacy (non-inferiority) between the 100 mg total daily dose and the 140 mg total daily dose (difference in MCyR -0.8%; 95% confidence interval [-9.6%–8.0%]). Since the minimum follow-up was only 6 months, there were too few progressions to estimate the duration of MCyR.

Table 10: Efficacy of SPRYCEL in Phase 3 Dose-Optimization Study (Chronic Phase CML)

	100 mg QD (N=167)	50 mg BID[a] (N=168)	140 mg QD[a] (N=167)	70 mg BID[a] (N=168)
Hematologic Response Rate[b] (%)				
CHR	90%	92%	86%	87%
Cytogenetic Response[c] (%)				
MCyR				
All patients (95% CI)	59% (51–66)	54% (46–61)	56% (48–63)	55% (48–63)
Imatinib-resistant patients (95% CI) (n/N)	53% (44–62) (66/124)	47% (38–56) (58/124)	50% (41–60) (62/123)	51% (42–60) (65/127)
CCyR				
All patients	41%	42%	44%	45%
Imatinib-resistant patients (95% CI) (n/N)	34% (26–43) (42/124)	35% (26–44) (43/124)	36% (27–45) (44/123)	39% (31–48) (50/127)

[a] Not a recommended starting dosage of SPRYCEL for chronic phase CML.

[b] Hematologic response criteria (confirmed after 4 weeks):

CHR (chronic CML): WBC ≤ institutional ULN, platelets <450,000/mm^3, no blasts or promyelocytes in peripheral blood, <5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood <20%, and no extramedullary involvement.

[c] Cytogenetic response criteria: complete (0% Ph+ metaphases) or partial (>0%–35%). MCyR (0%–35%) combines both complete and partial responses.

15 REFERENCES

1. Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings. NIOSH Alert 2004-165.

2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999, http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html.

3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm*. (2006) 63:1172-1193.

4. Polovich, M., White, J. M., Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

SPRYCEL® (dasatinib) tablets are available as described in Table 11.

Table 11: SPRYCEL Trade Presentations

NDC Number	Strength	Description	Tablets per Bottle
0003-0527-11	20 mg	white to off-white, biconvex, round, film-coated tablet with "BMS" debossed on one side and "527" on the other side	60
0003-0528-11	50 mg	white to off-white, biconvex, oval, film-coated tablet with "BMS" debossed on one side and "528" on the other side	60
0003-0524-11	70 mg	white to off-white, biconvex, round, film-coated tablet with "BMS" debossed on one side and "524" on the other side	60

16.2 Storage

SPRYCEL tablets should be stored at 25° C (77° F); excursions permitted between 15°–30° C (59°–86° F) [see USP Controlled Room Temperature].

16.3 Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published *[see References (15)]*.

SPRYCEL (dasatinib) tablets consist of a core tablet (containing the active drug substance), surrounded by a film coating to prevent exposure of pharmacy and clinical personnel to the active drug substance. However, if tablets are crushed or broken, pharmacy and clinical personnel should wear disposable chemotherapy gloves. Personnel who are pregnant should avoid exposure to crushed or broken tablets.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.1).

17.1 Bleeding

Patients should be informed of the possibility of serious bleeding and to report immediately any signs or symptoms suggestive of hemorrhage (unusual bleeding or easy bruising).

17.2 Myelosuppression

Patients should be informed of the possibility of developing low blood cell counts; they should be instructed to report immediately should fever develop, particularly in association with any suggestion of infection.

17.3 Fluid Retention

Patients should be informed of the possibility of developing fluid retention (swelling, weight gain, or shortness of breath) and to seek medical attention if those symptoms arise.

17.4 Pregnancy

Patients should be informed that dasatinib may cause fetal harm when administered to a pregnant woman. Women should be advised of the potential hazard to the fetus and to avoid becoming pregnant. If SPRYCEL is used during pregnancy, or if the patient becomes pregnant while taking SPRYCEL, the patient should be apprised of the potential hazard to the fetus *[see Warnings and Precautions (5.5)]*.

17.5 Gastrointestinal Complaints

Patients should be informed that they may experience nausea, vomiting or diarrhea with SPRYCEL. If these symptoms are significant, they should seek medical attention.

17.6 Pain

Patients should be informed that they may experience headache or musculoskeletal pain with SPRYCEL. If these symptoms are significant, they should seek medical attention.

17.7 Fatigue

Patients should be informed that they may experience fatigue with SPRYCEL. If this symptom is significant, they should seek medical attention.

17.8 Rash

Patients should be informed that they may experience skin rash with SPRYCEL. If this symptom is significant, they should seek medical attention.

17.9 Lactose

Patients should be informed that SPRYCEL contains 135 mg of lactose monohydrate in a 100-mg daily dose and 189 mg of lactose monohydrate in a 140-mg daily dose.

Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

US Patent No 6,596,746

Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

1237674 Rev November 2007

17.10 FDA-Approved Patient Labeling

SPRYCEL® (dasatinib) Tablets

What is SPRYCEL?

SPRYCEL (dasatinib) is a prescription medicine used to treat adults who have chronic myeloid leukemia (CML) and to treat adults who have a particular form of acute lymphoblastic leukemia (ALL) called Philadelphia chromosome positive or Ph+ ALL. It is intended for use in patients who are no longer benefiting from treatment with the current available therapies for these diseases (resistance), including a medicine called

GLEEVEC® (imatinib mesylate). It may also be used in patients who experience severe side effects from GLEEVEC and are no longer able to take it (intolerance). The long-term benefits and toxicities of SPRYCEL are currently still being studied. SPRYCEL has not been studied in children.

What is Leukemia?

Leukemia is a cancer of white blood cells, which grow in the bone marrow. In leukemia, white blood cells multiply in an uncontrolled manner, occupying the bone marrow space and spilling out into the bloodstream. As a consequence, the production of normal red blood cells (oxygen carrying cells), white blood cells (cells which fight infection), and platelets (cells which help blood clot) is compromised. Therefore, patients with leukemia are at risk of serious anemia, infections, and bleeding.

Chronic myeloid leukemia or CML is one form of leukemia. In CML, *myeloid* white blood cells multiply in an uncontrolled manner. It may take years for CML to progress because it is a slow-growing or chronic cancer. As CML progresses, patients advance through three phases: chronic phase, accelerated phase, and blast crisis phase. Ph+ acute *lymphoblastic* leukemia or Ph+ ALL is another form of leukemia. Acute leukemias progress faster than chronic leukemias. In Ph+ ALL, lymphoblastic white blood cells multiply in an uncontrolled manner.

How does SPRYCEL work?

The active ingredient of SPRYCEL is dasatinib. Dasatinib reduces the activity of one or more proteins responsible for the uncontrolled growth of the leukemia cells of patients with CML or Ph+ ALL. This reduction allows the bone marrow to resume production of normal red cells, white cells, and platelets.

Who should not take SPRYCEL?

- SPRYCEL is currently not recommended for patients who have not previously had a trial of GLEEVEC® (imatinib mesylate).

- Women who are pregnant or planning to become pregnant should not take SPRYCEL (see below).

What should I tell my healthcare provider before I take SPRYCEL?

Tell your healthcare provider about all of your medical conditions, including if you:

- **are pregnant or planning to become pregnant.** SPRYCEL may harm the fetus when given to a pregnant woman. Women should avoid becoming pregnant while undergoing treatment with SPRYCEL. Tell your healthcare provider *immediately* if you become pregnant or plan to become pregnant while taking SPRYCEL.

- **are breast-feeding.** It is not known if SPRYCEL can pass into your breast milk or if it can harm your baby. Do not breast-feed if you are taking SPRYCEL.

- **are a sexually active male.** Men who take SPRYCEL are advised to use a condom to avoid pregnancy in their partner.

- have a liver or heart problem.

- are lactose intolerant.

Can I take other medicines with SPRYCEL?

Tell your healthcare provider about all the medicines you take including prescription and over-the-counter medicines, vitamins, antacids, and herbal supplements.

SPRYCEL is eliminated from your body through the liver. The use of certain other medicines may alter the levels of SPRYCEL in your bloodstream. Likewise, levels of other medicines in your bloodstream can be affected by SPRYCEL. Such changes can increase the side effects, or reduce the activity of the medicines you are taking, including SPRYCEL.

- Medicines that increase the amount of SPRYCEL in your bloodstream are NIZORAL® (ketoconazole), SPORANOX® (itraconazole), NORVIR® (ritonavir), REYATAZ® (atazanavir sulfate), CRIXIVAN® (indinavir), VIRACEPT® (nelfinavir), INVIRASE® (saquinavir), KETEK® (telithromycin), E-MYCIN® (erythromycin), and BIAXIN® (clarithromycin).

- Medicines that decrease the amount of SPRYCEL in your bloodstream are DECADRON® (dexamethasone), DILANTIN® (phenytoin), TEGRETOL® (carbamazepine), RIMACTANE® (rifampin), and LUMINAL® (phenobarbital).

- Medicines whose blood levels might be altered by SPRYCEL are SANDIMMUNE® (cyclosporine), ALFENTA® (alfentanil), FENTANYL® (fentanyl), ORAP® (pimozide), RAPAMUNE® (sirolimus), PROGRAF® (tacrolimus), and ERGOMAR® (ergotamine).

SPRYCEL is best absorbed from your stomach into your bloodstream in the presence of stomach acid. You should avoid taking medicines that reduce stomach acid such as TAGAMET® (cimetidine), PEPCID® (famotidine), ZANTAC® (ranitidine), PRILOSEC® (omeprazole), PROTONIX® (pantoprazole sodium), NEXIUM® (esomeprazole), ACIPHEX® (rabeprazole), or PREVACID® (lansoprazole) while taking SPRYCEL. Medicines that neutralize stomach acid, such as MAALOX® (aluminum hydroxide/magnesium hydroxide), TUMS® (calcium carbonate), or ROLAIDS® (calcium carbonate and magnesia) may be taken up to 2 hours before or 2 hours after SPRYCEL.

Since SPRYCEL therapy may cause bleeding, tell your healthcare provider if you are using blood thinners, such as COUMADIN® (warfarin sodium) or aspirin.

How should I take SPRYCEL?

- If you have chronic phase CML, the usual dose is 100 mg (two 50-mg tablets) once daily, either in the morning or in the evening.

- If you have accelerated or blast crisis CML or Ph+ ALL, the usual dose is 70 mg (one 70-mg tablet) twice daily, once in the morning and once in the evening.

- SPRYCEL can be taken with or without a meal. Try to take SPRYCEL at the same time each day.

- Take SPRYCEL whole. Do not break, cut, or crush the tablets.

- Do not drink grapefruit juice while taking SPRYCEL.

- **Depending on your response to treatment and any side effects that you may experience, your healthcare provider may adjust your dose of SPRYCEL upward or downward, or may temporarily discontinue SPRYCEL.**

- **You should not change your dose or stop taking SPRYCEL without first talking with your healthcare provider.**

- **If you miss a dose of SPRYCEL**, take your next scheduled dose at its regular time. Do not take two doses at the same time. Call your healthcare provider or pharmacist if you are not sure what to do.

- **If you accidentally take more than the prescribed dose of SPRYCEL**, call your healthcare provider right away.

What are the possible side effects of SPRYCEL?

The following information describes the most important side effects of SPRYCEL. It is not a comprehensive list of all side effects recorded in clinical trials with SPRYCEL. You should report any unusual symptoms to your healthcare provider.

- **Low Blood Counts:** SPRYCEL may cause low red blood cell counts (anemia), low white blood cell counts (neutropenia), and low platelet counts (thrombocytopenia). Your healthcare provider will monitor your blood counts frequently after you start SPRYCEL and may adjust your dose of SPRYCEL or withhold the drug temporarily in the event your blood counts drop too low. In some cases, you may need to receive transfusions of red blood cells or platelets. **Notify your healthcare provider immediately if you develop a fever while taking SPRYCEL.**

- **Bleeding:** SPRYCEL may cause bleeding. The most serious bleeding events observed in clinical studies included bleeding into the brain leading to death in <1% of patients, and bleeding from the gastrointestinal tract. Less severe events included bleeding from the nose, the gums, bruising of the skin, and excessive menstrual bleeding. **Notify your healthcare provider immediately if you experience bleeding or easy bruising while taking SPRYCEL.**

- **Fluid Retention:** SPRYCEL may cause fluid to accumulate in your legs and around your eyes. In more severe cases, fluid may accumulate in the lining of your lungs, the sac around your heart, or your abdominal cavity. **Notify your healthcare provider immediately if you experience swelling, weight gain, or increasing shortness of breath while taking SPRYCEL.**

Other common side effects of SPRYCEL therapy include diarrhea, headache, skin rash, nausea, fatigue, and shortness of breath.

In clinical trials of 2182 patients, 10% (10 out of 100) of patients permanently stopped SPRYCEL therapy because of side effects.

How will I know if SPRYCEL is working?

How well you respond to SPRYCEL therapy may depend on several factors, including the phase of your disease, prior treatments, or other factors your healthcare provider may discuss with you. General treatment goals for patients treated with SPRYCEL include a reduction in the number of leukemia cells and improvement or normalization of the white blood cell, red blood cell, and platelet counts.

While you are on SPRYCEL, your healthcare provider will monitor these responses through routine blood tests. The type and frequency of these tests will be determined by your healthcare provider and may vary depending on the status of your disease.

How should I store SPRYCEL?

- Store SPRYCEL (dasatinib) Tablets at room temperature, 59° to 86° F (15° to 30° C). SPRYCEL Tablets do not require refrigeration.
- Keep the container tightly closed.
- Throw away SPRYCEL when it is outdated. Ask your pharmacist how to properly dispose of SPRYCEL.
- **Keep SPRYCEL and all medicines out of the reach of children and pets.**

General information about SPRYCEL: This medicine was prescribed for your particular condition and should be used only by you under the close supervision of your healthcare provider. The leaflet summarizes the most important information about SPRYCEL. If you would like more information, talk with your healthcare provider. If you have questions or concerns, or want more information about SPRYCEL, your healthcare provider and pharmacist have the complete prescribing information upon which this guide is based. You may want to read it and discuss it with your healthcare provider. Remember, no written summary can replace careful discussion with your healthcare provider.

What are the ingredients in SPRYCEL?

Active Ingredient: dasatinib

Inactive Ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The tablet coating consists of hypromellose, titanium dioxide, and polyethylene glycol.

Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

US Patent No 6,596,746

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Princeton, NJ 08543 USA

1237674 Rev November 2007

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-986/S001 & 002

SUMMARY REVIEW

Division Director Summary Review of NDA Supplements

NDA: 21-986/S-001 and S-002
Applicant: Bristol-Myers Squibb Company
Drug: SPRYCEL® (dasatinib) Tablets
Date: November 8, 2007

In June 2006 dasatinib was approved for the following indications:

> SPRYCEL® (dasatinib) is indicated for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy including imatinib. The effectiveness of SPRYCEL is based on hematologic and cytogenetic response rates. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.
>
> SPRYCEL is also indicated for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.

These supplements request approval of a new dosing regimen for chronic phase chronic myeloid leukemia (S-001), and the inclusion of the results of a randomized phase 2 study in the package insert (S-002).

S-001

The design and results of the phase 3 dose-optimization study are summarized in the following excerpts from the agreed-upon package insert:

> A randomized, open-label study was conducted in patients with chronic phase CML, whose disease was resistant to or who were intolerant to imatinib, to evaluate the efficacy of SPRYCEL administered once daily compared with SPRYCEL administered twice daily. Patients with significant cardiac diseases including myocardial infarction within 6 months, congestive heart failure within 3 months, significant arrhythmias, or QTc prolongation were excluded from the study. The primary endpoint was MCyR in patients with imatinib-resistant chronic phase CML. The main secondary endpoint was MCyR by total daily dose level in the same population. A total of 670 patients, of whom 498 had imatinib resistant disease, were randomized to the SPRYCEL 100 mg once daily, 140 mg once daily, 50 mg twice daily, or 70 mg twice daily group. Minimum follow-up was 6 months and median duration of treatment was approximately 8 months.

Response rates are presented in Table 10. Efficacy was achieved across all SPRYCEL treatment groups with the once daily schedule demonstrating comparable efficacy (non-inferiority) to the twice daily schedule on the primary efficacy endpoint (difference in MCyR 2.8%; 95% confidence interval [-6.0%–11.6%]). The main secondary endpoint of the study also showed comparable efficacy (non-inferiority) between the 100 mg total daily dose and the 140 mg total daily dose (difference in MCyR -0.8%; 95% confidence interval [-9.6%–8.0%]). Since the minimum follow-up was only 6 months, there were too few progressions to estimate the duration of MCyR.

Table 10: Efficacy of SPRYCEL in Phase 3 Dose-Optimization Study (Chronic Phase CML)

	100 mg QD (N=167)	50 mg BID[a] (N=168)	140 mg QD[a] (N=167)	70 mg BID[a] (N=168)
Hematologic Response Rate[b] (%)				
CHR	90%	92%	86%	87%
Cytogenetic Response[c] (%)				
MCyR				
All patients (95% CI)	59% (51–66)	54% (46–61)	56% (48–63)	55% (48–63)
Imatinib-resistant patients (95% CI) (n/N)	53% (44–62) (66/124)	47% (38–56) (58/124)	50% (41–60) (62/123)	51% (42–60) (65/127)
CCyR				
All patients	41%	42%	44%	45%
Imatinib-resistant patients (95% CI) (n/N)	34% (26–43) (42/124)	35% (26–44) (43/124)	36% (27–45) (44/123)	39% (31–48) (50/127)

[a] Not a recommended starting dosage of SPRYCEL for chronic phase CML.

[b] Hematologic response criteria (confirmed after 4 weeks):
CHR (chronic CML): WBC ≤ institutional ULN, platelets <450,000/mm^3, no blasts or promyelocytes in peripheral blood, <5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood <20%, and no extramedullary involvement.

[c] Cytogenetic response criteria: complete (0% Ph+ metaphases) or partial (>0%–35%). MCyR (0%–35%) combines both complete and partial responses.

In this study the median duration of therapy was approximately 12 months (range <1–20 months). The rate of discontinuation for adverse reactions was lower in patients treated with 100 mg once daily than in patients treated with 70 mg twice daily (4% and 12%, respectively). Selected adverse reactions are shown by dose regimen in Table 4.

Table 4: Selected Adverse Reactions Reported in Phase 3 Dose-Optimization Study (Chronic Phase CML)

	100 mg QD (n=165)		140 mg QD[a] (n=163)		50 mg BID[a] (n=167)		70 mg BID[a] (n=167)	
	All Grades	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Preferred Term	**Percent (%) of Patients**							
Diarrhea	23	1	26	3	26	3	25	4
Fluid Retention	24	2	33	4	27	4	32	5
Superficial localized edema	14	0	14	1	14	0	16	0
Pleural effusion	10	2	20	2	16	3	18	2
Generalized edema	2	0	3	0	0	0	1	0
Congestive heart failure/cardiac dysfunction[b]	0	0	2	1	1	1	4	2
Pericardial effusion	1	1	4	1	2	1	2	1
Pulmonary edema	0	0	0	0	1	0	2	1
Pulmonary hypertension	0	0	0	0	0	0	1	1
Hemorrhage	10	1	12	1	9	2	14	2
Gastrointestinal bleeding	1	1	2	0	4	2	4	2

[a] Not a recommended starting dosage of SPRYCEL for chronic phase CML.

[b] Includes left ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and ventricular failure.

Laboratory abnormalities reported in this study are shown in Table 6.

Table 6: CTC Grades 3/4 Laboratory Abnormalities in Phase 3 Dose-Optimization Study (Chronic Phase CML)

	100 mg QD (n=165)	140 mg QD[a] (n=163)	50 mg BID[a] (n=167)	70 mg BID[a] (n=167)
	Percent (%) of Patients			
Hematology Parameters				
Neutropenia	34	43	46	43
Thrombocytopenia	22	40	34	38
Anemia	10	19	18	17
Biochemistry Parameters				
Hypophosphatemia	8	6	7	7
Hypocalcemia	2	3	1	2
Elevated SGPT (ALT)	0	1	1	1
Elevated SGOT (AST)	1	1	0	0
Elevated Bilirubin	1	2	0	1
Elevated Creatinine	0	1	0	1

[a] Not a recommended starting dosage of SPRYCEL for chronic phase CML.

CTC grades: neutropenia (Grade 3 ≥0.5–1.0 × 10^9/L, Grade 4 <0.5 × 10^9/L); thrombocytopenia (Grade 3 ≥10–50 ×10^9/L, Grade 4 <10 × 10^9/L); anemia (hemoglobin ≥65–80 g/L, Grade 4 <65 g/L); elevated creatinine (Grade 3 >3–6 × upper limit of normal range (ULN), Grade 4 >6 × ULN); elevated bilirubin (Grade 3 >3–10 × ULN, Grade 4 >10 × ULN); elevated SGOT or SGPT (Grade 3 >5–20 × ULN, Grade 4 >20 × ULN); hypocalcemia (Grade 3 <7.0–6.0 mg/dL, Grade 4 <6.0 mg/dL); hypophosphatemia (Grade 3 <2.0–1.0 mg/dL, Grade 4 <1.0 mg/dL).

S-002

The design and results of the randomized phase 2 study in patients with chronic phase CML are summarized below:

A randomized, open-label study was conducted in patients whose disease was resistant to prior imatinib therapy at doses of 400 or 600 mg. The primary endpoint was MCyR at 12 weeks. One hundred fifty patients were randomized in a 2:1 ratio to either SPRYCEL 70 mg twice daily or imatinib 800 mg daily (400 mg twice daily). Crossover to the alternate therapy was permitted in the event of disease progression or intolerable toxicity. Median follow-up was 15 months. Median duration of treatment prior to crossover was 14 months for SPRYCEL and 3 months for imatinib.

Prior to crossover, 93% of the SPRYCEL-treated patients and 82% of the imatinib-treated patients achieved a CHR. At 12 weeks, MCyR was achieved in 36% of the SPRYCEL-treated patients (CCyR in 22%) and 29% of the imatinib-treated patients (CCyR in 8%). With longer treatment and follow-up, MCyR was achieved in 52% of the SPRYCEL-treated patients (CCyR in 40%) and 33% of the imatinib-treated patients (CCyR in 16%) prior to crossover. Since

the median follow-up was 15 months, there were too few progressions to reliably estimate the duration of MCyR.

In this study, 101 patients received SPRYCEL (starting dosage 70 mg twice daily) and 49 patients received imatinib (starting dosage 800 mg daily [400 mg twice daily]). Crossover to the alternate therapy was permitted. The median duration of therapy prior to crossover was longer for SPRYCEL (19 months) than for imatinib (3 months). Selected adverse reactions are presented in Table 3.

Table 3: Selected Adverse Reactions in Phase 2 Randomized Study (Chronic Phase CML)

	SPRYCEL[a] (n=101)		Imatinib[a] (n=49)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Preferred Term	Percent (%) of Patients			
Diarrhea	37	2	29	2
Fluid Retention	36	7	43	0
Pleural effusion	23	5	0	0
Superficial localized edema	17	1	41	0
Generalized edema	2	0	4	0
Congestive heart failure/cardiac dysfunction[b]	2	1	0	0
Pericardial effusion	1	0	0	0
Pulmonary edema	3	2	0	0
Pulmonary hypertension	1	0	0	0
Nausea	24	0	33	0
Hemorrhage	18	1	8	0
Gastrointestinal bleeding	3	1	0	0
Vomiting	10	0	24	0

[a] Starting dosage: SPRYCEL 70 mg twice daily; imatinib 800 mg daily (400 mg twice daily).

[b] Includes left ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and ventricular failure.

The frequency of Grade 3 or 4 neutropenia, thrombocytopenia, and anemia was 63%, 56%, and 19%, respectively, in the SPRYCEL group and 39%, 14%, and 8%, respectively, in the imatinib group. The frequency of Grade 3 or 4 hypocalcemia was 4% in the SPRYCEL group and 0% in the imatinib group.

Clinical Reviews

The Clinical Review made the following recommendation on approvability:

> This dasatinib sNDA 021986, submitted on May 11, 2007, provided adequate evidence supporting a new dose and schedule of dasatinib, 100 mg once daily, for the treatment of patients with chronic phase (CP) Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) with resistance or intolerance to

> imatinib. The reviewer concurs with the submitted data and the Sponsor's analyses of the data for this sNDA. Since dasatinib has been approved for the same indication, the new dose schedule should improve patient's tolerability and reduce the key dasatinib-associated adverse reactions, without significant decline in treatment responses. The balance of benefit/risk of the new dose schedule should be carefully monitored by health care providers, and dose adjustment may still be needed based on patient's response and tolerance. Due to the fact that no long-term data exists using this regimen, the reviewer recommends accelerated approval of this new dose and schedule of dasatinib for the treatment of patients with chronic phase chronic myeloid leukemia resistant to or who are intolerant to prior therapy including imatinib. The Sponsor must provide additional follow-up to convert to regular approval.

The review made the following recommendation on phase 4 studies:

> Since the dose-schedule optimizing study CA180034 is still ongoing and the overall follow-up time is still short, about 11~12 months, the long-term efficacy and safety profile of the study should be obtained and reported to the FDA after the completion of the study.

The Deputy Division Director/Clinical Team Leader Review made the following recommendation:

> This application is recommended for accelerated approval due to the fact that we do not have sufficient information on durability of response with the reduced dose regimen. In the approved PLR labeling the sponsor has incorporated the lower dosing regimen and schedule for patients with CP CML.

Statistical Review and Evaluation

The Statistical Review and Evaluation had the following conclusions and recommendations:

> The applicant submitted the data and analyses of two trials, CA180034 and CA180017 (mainly for updating the report submitted in the initial NDA), to seek a change in the dose and administration schedule for dasatinib in the treatment of subjects with chronic phase CML. The data and analyses in this supplemental NDA #21,986 demonstrated that the efficacy of dasatinib when administered QD was similar to that administered BID in the treatment of subjects with chronic phase CML and support a change in the dose and administration schedule for dasatinib in the treatment of subjects with chronic phase CML.

Clinical Pharmacology Review

The Clinical Pharmacology Review made labeling recommendations regarding the conversion to PLR format.

Chemistry Review

The Chemistry Review stated that "The request for exclusion from the requirement for an Environmental Assessment is justified."

Conclusion

I concur with the recommendations for approval of these two supplements. Study CA-180-034 submitted in support of S-001 provides for a lower dose for patients with chronic phase CML with resistance or intolerance to prior therapy including imatinib. The dose of 100 mg/day appears to be as effective as the previously approved dose of 70 mg twice daily and is associated with less toxicity. However the follow-up is short and it has not yet been established that the responses seen with the lower dose will be of the same duration as the originally approved dose. For this reason the following postmarketing commitment, which was not originally a condition of the accelerated approval, has been converted to a subpart H postmarketing commitment:

> 7. You have agreed to submit the completed study report (24 month follow-up) and data from the study, CA-180-034, a randomized, two-by-two, open-label study of dasatinib (BMS-354825) in subjects with Chronic Phase Philadelphia Chromosome Positive Chronic Myeloid Leukemia resistant to or intolerant of Imatinib Mesylate.
>
> Protocol Submission: 04/2005
> Study Start: 07/2005
> Final Report Submission: 06/2009

The randomized phase 2 trial submitted in support of S-002 provides additional useful information regarding the comparative safety and efficacy of dasatinib 70 mg twice daily vs. high dose imatinib (400 mg twice daily) in patients whose disease was resistant to prior imatinib therapy at doses of 400 or 600 mg.

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

Robert Justice
11/8/2007 05:29:51 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-986/S001 & 002

MEDICAL REVIEW(S)

Deputy Division Director/Clinical Team Leader Review of NDA 21986s001-2
Drug: Sprycel® (dasatinib)
Applicant: Bristol-Myers Squibb Corporation
Date: October 20, 2007

SUMMARY

On May 11, 2007, the applicant submitted a New Drug Application for Sprycel® with a new dose and dose schedule recommendation for the treatment of patients with chronic phase chronic myelogenous leukemia (CP CML) whose disease is resistant to imtainib or for patients who are unable to tolerate dose escalation of imantinib due to toxicity to treat their disease.

The submission contains 2 studies. The first study is an international, multicenter, randomized study with a 2 x 2 design which evaluates 2 questions regarding dasatinib dosing in patients with CP CML. The first is whether the once daily (QD) dosing is as efficacious as the twice daily (BID) dosing. The second is whether receiving 100 mg as a total daily dose is as efficacious as receiving 140 mg as a total daily dose.

The study had 4 treatment arms: 100 mg QD, 50 mg BID, 140 mg QD, and 70 mg BID (currently recommended dose). Approximately 170 patients were enrolled in each of the 4 treatment arms. Demographics and disease characteristics were balanced among the treatment arms. The results of the study suggest that the 100 mg QD dosing has comparable efficacy to the 70 mg BID dose (currently labeled dosing recommendation). This conclusion is based on the fact that the major cytogenetic response (MCyR) for the 100 mg QD dose was close to the result demonstrated for the currently labeled dose. The sponsor performed several analyses looking at comparability. Please see Dr. He's statistical review for details.

The sponsor's table from the label is reproduced below.

Table 10: Efficacy of SPRYCEL in Phase 3 Dose-Optimization Study (Chronic Phase CML)

	100 mg QD n=167	50 mg BID[a] n=168	140 mg QD[a] n=167	70 mg BID[a] n=168
			b (4)	
Hematologic Response Rate[b] (%)				
CHR	90%	92%	86%	87%
Cytogenetic Response[c] (%)				
MCyR				
All patients (95% CI)	59% (51-66)	54 %(46-61)	56% (48-63)	55% (48-63)
Imatinib-resistant patients (95% CI) (n/N)	53% (44-62) (66/124)	47% (38-56) (58/124)	50% (41-60) (62/123)	51% (42-60) (65/127)
CCyR				
All patients	41%	42%	44%	45%
Imatinib-resistant patients (95% CI) (n/N)	34% (26-43) (42/124)	35% (26-44) (43/124)	36% (27-45) (44/123)	39%(31-48) (50/127)

a Not a recommended starting dosage of SPRYCEL for chronic phase CML.

b Hematologic response criteria (confirmed after 4 weeks):
CHR (chronic CML): WBC ≤ institutional ULN, platelets <450,000/mm^3, no blasts or promyelocytes in peripheral blood, <5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood <20%, and no extramedullary involvement.

c Cytogenetic response criteria: complete (0% Ph+ metaphases) or partial (>0%–35%). MCyR (0%–35%) combines both complete and partial responses.

In addition, the 100 mg daily dose was associated with lower toxicity compared to 70 mg twice daily dosing, particularly for myelosuppression and pleural effusions. For details please see the primary medical review by Dr. Yang-Min Ning and the statistical review by Dr. Kun He.

Reviewer Comment: This comparability is not unexpected as responses were seen with dasatinib in the original NDA with doses as low as 30 mg QD. Based on Agency review of the new submission, this information regarding efficacy and safety with the lower dose will be incorporated into the labeling.

The second study is a randomized trial comparing dasatinib 70 mg twice daily with imatinib at 800 mg daily in patients with CP CML who are no longer responsive to imatinib at 400-600 mg daily. Patients were randomized 2:1 to dasatinib or imatinib. The primary endpoint of the trial was the MCyR at 12 weeks. The MCyR 12 week results were: 36% and 29% respectively. The complete cytogenetic response (CCyR) results were: 22% and 8% respectively. With longer follow up the MCyR results were: 52% and

33%. For additional details, please see the primary medical review by Dr. Yang-Min Ning.

Dr. Ning performed an assessment of efficacy by age using the following categories: < 65 years of age and ≥65 years of age. This result differs with a similar analysis performed on data submitted in the original NDA. Information regarding Dr. Ning's analysis will be placed in the label.

In addition to the studies above, the sponsor submitted a request for an exclusion for the Environmental Assessment. The sponsor also submitted PLR labeling. The Chemistry review team agreed with the request for exclusion.

During the review process, the sponsor submitted a study that was part of their phase 4 commitments from the original approval letter. This study assessed the effects of the co-administration of dasatinib with ketoconazole. The Clinical Pharmacology review team reviewed the data and agreed that the sponsor has fulfilled the following from the original approval:

> *You have agreed to submit the complete study report and data from the study, CA-180-021, an open-label, single-sequence study to evaluate the effect of ketoconazole on the pharmacokinetics of BMS-354825 in patients with advanced solid tumors.*
> *Protocol Submission: 03/2005*
> *Study Start: 07/2005*
> *Final Report Submission: 12/2006*

The information from this study has been incorporated into the new PLR labeling.

Conclusion: This application is recommended for accelerated approval due to the fact that we do not have sufficient information on durability of response with the reduced dose regimen. In the approved PLR labeling the sponsor has incorporated the lower dosing regimen and schedule for patients with CP CML.

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/s/

Ann Farrell
11/8/2007 08:07:45 AM
MEDICAL OFFICER

Application Type:	**sNDA Dasatinib**
Submission Number:	021986
Submission Code:	
Letter Date:	May 10, 2007
Stamp Date:	
PDUFA Goal Date:	Nov 11, 2007
Medical Reviewer:	Yangmin M Ning M.D., Ph.D.
Medical Team Leader:	Ann T Farrell M.D.
Review Completion Date:	Oct 31, 2007
Established Name:	Dasatinib
Therapeutic Class:	Anti-neoplastic tyrosine kinase inhibitor
Applicant:	Bristol-Myers Squibb company
Priority Designation:	Priority Review
Dosing Regimen:	Dasatinib is recommended to be administered orally at a dose of 100 mg once daily.
Indication:	Chronic phase chronic myeloid leukemia
Intended Population:	Adults with chronic phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib

Table of Contents

Table of Tables and Figures

Commonly used abbreviations in the review

Abbreviation	Full Term
AR	Adverse Reaction
BID	Bis In Die
CBC	Complete Blood Count
CCyR	Complete Cytogenetic Response
CHR	Complete Hematologic Response
CML	Chronic Myelogenous Leukemia
CP	Chronic Phase
DRAR	Drug-Related Adverse Reaction
ECG	Electrical Cardiogram
MCyR	Major Cytogenetic Response (defined as CCyR plus PCyR)
PCyR	Partial Cytogenetic Response
OS	Overall Survival
PFS	Progression Free Survival
Ph+	Philadelphia Chromosome Positive
QD	Quaque Die
TDD	Total Daily Dose
TEAR	Treatment-Emergent Adverse Reaction

Executive Summary Section

Clinical Review for sNDA 021986

Executive Summary

I. Recommendations

A. Recommendation on Approvability

This dasatinib sNDA 021986, submitted on May 11, 2007, provided adequate evidence supporting a new dose and schedule of dasatinib,100 mg once daily, for the treatment of patients with chronic phase (CP) Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) with resistance or intolerance to imatinib. The reviewer concurs with the submitted data and the Sponsor's analyses of the data for this sNDA. Since dasatinib has been approved for the same indication, the new dose schedule should improve patient's tolerability and reduce the key dasatinib-associated adverse reactions, without significant decline in treatment responses. The balance of benefit/risk of the new dose schedule should be carefully monitored by health care providers, and dose adjustment may still be needed based on patient's response and tolerance. Due to the fact that no long-term data exists using this regimen, the reviewer recommends accelerated approval of this new dose and schedule of dasatinib for the treatment of patients with chronic phase chronic myeloid leukemia resistant to or who are intolerant to prior therapy including imatinib. The Sponsor must provide additional follow-up to convert to regular approval.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

Since the dose-schedule optimizing study CA180034 is still ongoing and the overall follow-up time is still short, about 11~12 months, the long-term efficacy and safety profile of the study should be obtained and reported to the FDA after the completion of the study.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Dasatinib received accelerated approval on June 28, 2006 for the treatment of adult patients with chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib. The initial recommended dose schedule was 70 mg twice a day. However, this dose schedule was

found to be associated with frequent dose interruptions and reductions due to considerable myelosuppression and fluid retention, especially pleural effusion, resulting in a median actual average daily dose close to 100 mg/day in prior clinical trials. Since the effectiveness of dasatinib, with fewer adverse reactions, was also observed in patients receiving lower doses of dasatinib, optimizing dosing regimen of dasatinib became an important issue for a better risk/benefit ratio and compliance with a long-term therapy in patients with CML. The key study, CA180034, submitted in this sNDA, explored the possibility of establishing such an optimal dose and schedule for dasatinib.

CA180034 was an open-label, randomized Phase 3 study with a two-by-two factorial design to evaluate any differences in dasatinib efficacy/safety between two schedules (QD and BID) or two doses (100 mg and 140 mg) in patients with CP CML with resistance or intolerance to imatinib. A total of 670 patients were randomized approximately equally to each of the four dose schedules in this study, of which patients with imatinib-resistant disease were approximately 75% in each dose schedule. The median treatment time for each dose schedule was 11 months, with a minimum follow-up of 6 months. Efficacy evaluations are based on the data of the sNDA submission, whereas safety analyses are based on the data of the 120-day safety update.

In addition, the Sponsor submitted the data and preliminary results of another study CA180017, a randomized Phase 2 trial of dasatinib (70 mg BID) *vs* imatinib (400 mg BID) in patients with CP Ph+ CML whose disease was resistant to prior regular doses (400-600 mg/day) of imatinib. Its primary objective was to estimate MCyR rates at 12 weeks in the two arms. A total of 150 patients were randomized, 101 to the dasatinib arm and 49 to the imatinib arm. The minimal follow-up time was 12 months for both arms. The results of this study are not relevant to the proposed change in dasatinib dose and schedule, the main purpose of the current application.

B. Efficacy

The primary efficacy endpoint of CA180034 was to compare the rate of 6-month major cytogenetic response (MCyR) by schedule and dose. The results demonstrated that dasatinib administered at the QD schedules exhibited comparable MCyR rates compared to dasatinib administered at the BID schedules and that a total daily dose (TDD) of 100 mg was similar to a total daily dose of 140 mg in attaining a MCyR. The preliminary evidence also suggested that the duration of MCyR appeared to be similar by schedule and dose. Although there were 4~10% more patients in the 100 mg TDD arms, as compared to the 140 mg TDD arms, who required

dose escalation for lack of treatment responses, the efficacy results of this study are generally supportive of this new dose schedule, 100 mg QD, in treatment of patients with CP CML with resistance or intolerance to imatinib.

The results of CA180017 showed that the MCyR rate at 12 weeks was 36% in the dasatinib arm compared to 29% in the imatinib arm. With longer follow-up, the overall MCyR rate prior to crossover was 52% in the dasatinib arm compared to 33% in the imatinib arm. Patients who crossed over to the opposite arm after disease progression also had a higher MCyR rate with dasatinib treatment (44%) as compared with imatinib treatment (15%). These results suggest that dasatinib at 70 mg BID may be more active than the high dose imatinib of 800 mg/day in inducing a MCyR in patients with CP CML whose disease was resistant to conventional doses of imatinib.

C. Safety

Based on the 120-day safety update data of CA180034, the safety analyses of the four different dasatinib dose schedules (100 mg QD, 140 mg QD, 50 mg BID, and 70 mg BID) were performed. The results showed that the 100 mg QD, as compared to the other three dose schedules, was associated with lower incidences of pleural effusion, anemia, neutropenia, and thrombocytopenia, while most of other drug-related adverse reactions were generally comparable among the four dose schedules. Compared to the current recommended dose schedule 70 mg BID, the 100 mg QD dosing had at least 8% less occurrences of all Grade pleural effusion and Grade 3/4 thromobocytopenia and neutropenia. In addition, the lower rates of dose modifications and discontinuation due to adverse reactions (AR) were observed in the 100 mg QD schedule relative to the other three dose schedules. Overall, dosing dasatinib at 100 mg QD was associated with improved tolerability and safety of dasatinib in patients with CP CML with resistance or intolerance to imatinib.

The safety analyses of CA180017 on the data prior to crossover appeared to show that dasatinib, as compared to imatinib, was associated with higher incidences of most of observed hematologic and non-hematologic ARs. The shorter time of exposure to imatinib of 800 mg/day due to disease progression and the exclusion of patients intolerant to conventional doses of imatinib from enrollment likely contributed the safety differences in addition to the nature of the drugs.

D. Dosing

The proposed new dose schedule as follows:

Dasatinib is administered orally at a dose of 100 mg once daily. Tablets should not be crushed or cut, and should be swallowed whole.

E. Special Population

1) Pediatrics

   No pediatric patients were included in the randomized study.

2) Elderly

   Of the 670 patients randomized in CA180034, 179 (27%) were 65 years of age or older. Regardless of doses and schedules, the overall MCyR rate in this population of patients was 45%, compared to a MCyR rate of 60% in the patients <65 years old. The difference is 15% (95% CI: 6.7%~23.7%). Similar differences between the two age groups in MCyR rate exist in all fours dose schedules. In the 100 mg QD schedule, the MCyR rate was 14% less in patients ≥65, similar to that seen in the 70 mg BID schedule.

3) Gender

   The differences in gender-based MCyR rate appeared to be within 5% in CA180034, regardless of doses and schedules. Therefore, the new dose schedule appears to be applicable for genders.

4) Hepatic or Renal Impairment

   Dasatinib has not been evaluated in patients with hepatic or renal impairment. Therefore, use of dasatinib in patients with those problems is not supported by the data submitted.

5) Ethnicity

   No Race-based analyses on either efficacy or safety were performed because of small sample sizes of the minorities in this trial.

6) Pregnancy

   No pregnant subjects were included in this study.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Established Name: **Sprycel®**

Proprietary Name: **Dasatinib**

Applicant: **Bristol-Myers Squibb Company**
5 Research Parkway
P.O. Box 5100, Mailstop 3SIG-5014
Wallingford, CT 06492

Drug Class: **An inhibitor of multiple tyrosine kinases**

Indication:

a) Current:

- Chronic myeloid leukemia: Dasatinib is indicated for adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib. The effectiveness of dasatinib was based on hematologic and cytogenetic response rates. There were no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

- Acute lymphoblastic leukemia: Dasatinib is also indicated for adults with Philadelphia chromosome positive acute lymphoblastic leukemia with resistance or intolerance to prior therapy including imatinib.

b) Proposed: a new dose and schedule for the disease stage as follows

- Chronic phase chronic myeloid leukemia: 100 mg once daily, administered orally.

Dosage and Administration:

a) Current Label

The recommended dosage of dasatinib is 140 mg/day administered orally in two divided doses (70 mg twice daily), one in the morning and one in the evening with or without a meal. Tablets should not be crushed or cut; they should be swallowed whole.

- Dose Modification

Dose increase or reduction of 20-mg increments per dose is recommended based on individual safety and tolerability. Patients taking CYP3A4 inducers or inhibitors should be adjusted with a dose increase or a dose decrease of 20-40 mg daily accordingly.

Myelosuppression should be managed by dose interruption, dose reduction, or discontinuation of dasatinib with the guidelines as shown in Table 1.

Table 1: Dasatinib Dose Adjustment for Neutropenia and Thromobocytopenia (adopted from the previous dasatinib label)

Chronic Phase CML (starting dose 70 mg BID)	ANC* $<0.5 \times 10^9$/L and/or Platelets $<50 \times 10^9$/L	1. Stop SPRYCEL until ANC $\geq 1.0 \times 10^9$/L and platelets $\geq 50 \times 10^9$/L. 2. Resume treatment with SPRYCEL at the original starting dose. 3. If platelets $<25 \times 10^9$/L and/or recurrence of ANC $<0.5 \times 10^9$/L for >7 days, repeat Step 1 and resume SPRYCEL at a reduced dose of 50 mg BID (second episode) or 40 mg BID (third episode).
Accelerated Phase CML, Blast Phase CML and Ph+ ALL (starting dose 70 mg BID)	ANC $<0.5 \times 10^9$/L and/or Platelets $<10 \times 10^9$/L	1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukemia, stop SPRYCEL until ANC $\geq 1.0 \times 10^9$/L and platelets $\geq 20 \times 10^9$/L and resume at the original starting dose. 3. If recurrence of cytopenia, repeat Step 1 and resume SPRYCEL at a reduced dose of 50 mg BID (second episode) or 40 mg BID (third episode). 4. If cytopenia is related to leukemia, consider dose escalation to 100 mg BID.

*ANC: absolute neutrophil count

For severe non-hematological adverse reactions related with dasatinib use, treatment must be withheld until the event has

resolved or improved. Treatment can be resumed thereafter as appropriate at a reduced dose, depending on the initial severity of the event.

b) Proposed: *addition is as follows*

- The recommended starting dosage of dasatinib for chronic phase chronic myeloid leukemia is 100 mg administered once daily, either in the morning or in the evening. (note that the recommended dosage for other indications remains unchanged, 70 mg orally, twice daily).

B. State of Armamentarium for Indication

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder that accounts for 15-20% of all adult cases of leukemia. The vast majority of patients with CML have the Ph+ chromosome, the result of a chromosome translocation t(9; 22) which is characterized by an oncogenic fusion protein Bcr-Abl that induces leukemic transformation through the increased tyrosine kinase activity of the conjugated Abl. The disease is bi- or tri-phasic, an indolent chronic phase (CP) followed by one or two of aggressive transformed stages, accelerated phase (AC) and blast phase (BP), with a median survival time of 5~7 years [1] prior to the era of the revolutionary targeted therapy with imatinib, a specific Bcr-Abl tyrosine kinase inhibitor.

The natural course of the disease appears to be prolonged with targeted therapy, since the current evidence showed that imatinib was associated with 93% of patients free of progression to aggressive disease at 5 years [2]. This evidence also suggests that targeted therapy of CML is a long-term course for patients and that the tolerance and safety of a targeted agent are very important while the effectiveness of the agent is maintained during treatment.

Dasatinib received accelerated approval on June 28, 2006 for the treatment of adult patients with chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib. The recommended dose schedule was 70 mg twice a day. However, this dose schedule was associated with frequent dose interruptions and reductions due to considerable bone marrow suppression and fluid retention, especially pleural effusion, resulting in a median actual average daily dose close to 100 mg/day. Since cytogentic responses were also observed in some patients receiving lower doses in a Phase 1 study of dasatinib, and with fewer adverse reactions, a trial aimed to optimize dosing regimen of dasatinib was started 2 years ago in order to achieve a better benefit/risk

ratio and a superior compliance with a long-term therapy in patients with CP CML. In the current sNDA, the data and results of this trial were submitted, providing the first evidence for establishing such an optimized dose and schedule for dasatinib.

Review of literature suggests that pleural effusion appeared to be associated with different schedules, seen less frequently with once daily dosing compared to with twice daily schedule[3].

See IV D. Literature Review for the references supporting this section.

C. Important Milestones in Product Development

- March 11, 2003, the initial dasatinib investigational new drug application was submitted.
- June 28, 2006, accelerated approval for the treatment of adults with chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib. (original NDA 021986)
- June 28, 2006, regular approval for the treatment of adults with Philadelphia chromosome (Ph+)-positive acute lymphoblastic leukemia with resistance or intolerance to prior therapy. (original NDA 022072)
- May 11, 2007, sNDA submitted for a new recommended dose and administration schedule in the treatment of chronic phase chronic myeloid leukemia with resistance or intolerance to imatinib.

D. Other Relevant Information

None

E. Important Issues with Pharmacologically Related Agents

Imatinib is the first FDA-approved inhibitor against the tyrosine kinase activity of the Ph+ related oncogenic fusion protein Bcr-Abl and is indicated for the treatments of newly diagnosed chronic myeloid leukemia and several other malignant disorders. It has had 6 years of clinical experience in both its efficacy and safety since its approval in 2001. Overall, it is generally well tolerated and has been associated with a 5-year progression-free survival in 92.9% of patients with newly diagnosed chronic phase CML. [Approved imatinib label, Sep. 13, 2007]. Based on the safety surveillance results, one important safety update in the new label was to include severe congestive heart failure and left ventricular

dysfunction in the section of Warning and Precaution. This cardiac complication appeared to be particularly important for patients with prior cardiovascular comorbidities and risk factors [4]. The pathological evidence based on the myocardial biopsies of two patients who developed significant imatinib-associated left ventricular dysfunction showed prominent cell membrane abnormalities, suggestive of toxin-induced cardiomyopathies[5]. Further laboratory studies implied that the imatinib-induced cardiac toxicities observed in animals may be associated with the inhibition of the tyrosine kinase activity of normal cardiac Abl [5]. These observations raise a question if the agents targeting on Bcr-Abl tyrosine kinase activity exert a class effect on cardiac function. Therefore, close monitoring and evaluation of cardiac safety would be important for use of Bcr-Abl tyrosine kinase inhibitors, especially in patients with prior cardiac histories and/or co-morbidities.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

A. Chemistry

The chemistry review team has recommended the approval of this supplement.

B. Clinical Pharmacology and Toxicology

No new information was provided with this submission.

III. Human Pharmacokinetics and Pharmacodynamics

Dasatinib is an inhibitor of multiple kinase tyrosine kinases. In addition to the inhibition against the Abl kinase of the fusion protein Bcr-Abl, it also inhibits other kinases such as SRC family, c-KIT, and PDGFRβ. Its activity in overcoming imatinib resistance may be related to its ability to bind to multiple conformations of the ABL kinase.

The pharmacokinetics of dasatinib have been evaluated in both patients with CML and healthy human volunteers. Following oral administration, dasatinib reaches its maximum plasma concentrations within 0.5-6 hours. It displays both dose proportional increases in AUC and linear elimination characteristics over the dose range of 15 mg to 240 mg/day. The overall mean terminal half-life of dasatinib is 3–5 hours. Food effects appeared to be less clinically relevant, since dasatinib mean AUC was mildly elevated following high-fat meal.

In distribution, dasatinib has an apparent volume of distribution of 2505 Liter. This large distribution volume suggested that the drug is extensively distributed in the extravascular space. Plasma protein binding of dasatinib and its active metabolite *in vitro* was approximately 96% and 93%,respectively, with no concentration dependence over the range of 100–500 ng/mL.

Dasatinib is extensively metabolized in the liver, primarily by the cytochrome P450 enzyme 3A4, the primary enzyme responsible for the formation of the active metabolite. In vitro assays showed that dasatinib was a weak time-dependent inhibitor of CYP3A4. Dasatinib also generated inactive oxidative metabolites. Although its active metabolite is equipotent to dasatinib, the metabolite only represents approximately 5% of the dasatinib AUC, suggesting that the active metabolite of dasatinib is unlikely to play a major role in the observed pharmacology of the drug.

With its metabolism route, dasatinib is eliminated primarily via the feces. Radioactive [^{14}C]-labeled test showed 85% of the administered radioactivity found in faces, with 4% detected in urine. Non-metabolized dasatinib accounted for 19% and 0.1% of the administered dose in feces and urine, respectively, with the remainder of the dose being metabolites.

The pharmacokinetics of dasatinib have no clinically relevant effects with age and gender; however, no information is currently available for patients with renal or hepatic insufficiency.

Drug-Drug Interactions

Dasatinib interactions with other drugs have been evaluated in a small group of patients and volunteers. Ketoconazole, a CYP3A4 inhibitor, increased the dasatinib Cmax and AUC moderately. Other CYP3A4 inhibitors (eg, itraconazole, erythromycin, clarithromycin, and several anti-HIV inhibitors) may also decrease metabolism and increase concentrations of dasatinib. In contrast, CYP3A4 Inducers such as rifampicin decreased the mean Cmax and AUC of dasatinib considerably.

Antacids (eg, general acid neutralizers, H2 blockers, and PPIs) can also reduce the bioavailability and adsorption of dasatinib, since dasatinib solubility is pH-dependent.

As a substrate of CYP3A4, dasatinib can also compete with other drugs for the same metabolism enzyme, thus affecting their plasma concentrations.

Clinical Review Section

IV. Description of Clinical Data and Sources

A. Overall Data

The dasatinib sNDA 021986 contains data for a new dose schedule of the drug in the treatment of patients with CP CML with resistance or intolerance to imatinib. To support the new schedule, the sponsor provided the results and data of CA180034, a Phase III, open-label, randomized multicenter international trial. In addition, the sponsor included the updated results and datasets of a randomized Phase II study CA180017 for revising the dasatinib label with respective to the effectiveness of dasatinib vs high dose of imatinib in CP CML resistant to the regular doses of imatinib. CA180017 was a part of the initial dasatinib NDA submission, but not used for the analyses due to the small sample size at that time. Therefore, the key evaluations for this dasatinib sNDA rely on the data of Study CA180034 to support the establishment of the new dose and schedule. These two studies are summarized briefly in Section IV.B.

B. Tables Listing of the Clinical Trials

Table 2: Trials Included in the 021986 sNDA

Study Number	Design	Primary Endpoint	Studied Disease	Treatment Arm	Subject Number	Outcome
CA180034	Phase 3, randomized (2 by 2), open-label, multicenter international study	Difference in MCyR rates at 6 months between QD and BID schedules	Imatinib-resistant CP CML or patients with CP CML who were intolerant to imatinib	Dasatinib orally at 100 mg, QD; 140 mg QD; 50 mg BID; or 70 mg BID	670 patients randomized approximately equally to one of the four arms	Data submitted
CA180017	Phase 2, open-label, 2:1 randomized, multicenter study	MCyR rates at 12 weeks	Imatinib-resistant CP CML	Dasatinib 70 mg BID po vs Imatinib 800 mg QD po	150 randomized (101 in the dasatinib arm; 49 in the imatinib arm)	Data submitted along with this sNDA

C. Postmarketing Experience

Included in the safety update.

D. Literature Review

1. S Faderl, M. Talpaz, Z Estrov, and H. M. Kantarjian: Chronic myelogenous leukemia: biology and therapy. Ann Intern Med. 131(3):207-19; 1999

2. B. J. Druker, F. Guilhot, S. O'Brien, R. A. Larson, (on behalf of the IRIS): Long-term benefits of imatinib for patients newly diagnosed with chronic myelogenous leukemia in chronic phase: The 5-year update from the IRIS study. Journal of Clinical Oncology, 2006 ASCO Annual Meeting Proceedings Part I. Vol 24, No. 18S (June 20 Supplement), 6506; 2006

3. A. Quintás-Cardama, H. Kantarjian, S. O'Brien, G. Borthakur, J. Bruzzi, et al: Pleural effusion in patients with chronic myelogenous leukemia treated with dasatinib after imatinib failure. Journal of Clinical Oncology: 25: 3908-3914; 2007

4. E. Atallah, J.-B. Durand, H. Kantarjian, and J. Cortes: Congestive heart failure is a rare event in patients receiving imatinib therapy. Blood: 110 (4):1233-1237; 2007

5. R. Kerkelä, L. Grazette, R. Yacobi, C. Iliescu, R. Patten, et al: Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. Nature Medicine: 12(8):908-16; 2006

V. Clinical Review Methods

A. How the Review was Conducted

Both efficacy and safety analyses were based on the datasets of study CA180034, study CA180017, and the pooled population of 2182 patients treated with dasatinib in clinical trials.

B. Overview of Materials Consulted in Review

The medical reviewer has reviewed the regulatory history of dasatinib, previous medical review for its approval, the electronic submission of this sNDA, relevant publications in relation to efficacy claims of the new dose and schedule and safety profile, and the sponsor's responses to the reviewer's questions in the 6 inquiries conveyed to the Sponsor during the review.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The main methods utilized for evaluating the quality and integrity of the data from CA180034 and CA180017 include examining the data across different relevant datasets submitted by the sponsor, conducting independent analyses on efficacy differences among the tested dose schedules with the help of the statistical reviewer, and investigating safety data and verifying the accuracy and appropriateness of the sponsor's tabulations and presentations in the proposed dasatinib label. Any significant discrepancies in analyses between the reviewer and the sponsor will be noted and discussed in relevant sections of the review. In addition, the case report forms were checked randomly against the pertinent datasets, particularly in subjects who had MCyR or who had serious adverse reactions associated with the important known side effects of dasatinib.

An audit by the Division of Scientific Investigation was considered not to be necessary as early audited studies in the original NDA suggested that a lower dose was efficacious.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

All subjects were consented prior to randomization. They were allowed to withdraw at their will.

E. Evaluation of Financial Disclosure

Disclosure of financial interests of the investigators involved in b (4) and b (4) was reported in the FDA form 3455. This disclosure was certified by Claude Nicaise, MD, the vice president for Global Development for the Sponsor. Of the approximately b (4) registered investigators who reported with the disclosure, b ( ) investigators (b (4) %) had outstanding financial conflicts; however, most of them were sub-investigators and were not involved in the studies due to administrative role or advised by the Sponsor to not conduct the studies. Therefore, financial conflicts appeared to be minimal in those studies. Given the study endpoints were based on bone marrow evaluation of cytogenetic response, the effect of financial conflicts on the outcome of the studies would be further minimized.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Clinical Review Section

The key study for this sNDA is CA180034, which was intended to support a new dose and schedule for dasatinib in the treatment of patients with CP CML with resistance or intolerance to imatinib. This study was an open-label, randomized (two-by-two), multicenter international phase 3 trial of dasatinib administered at four different dose schedules (100 mg QD, 140 mg QD, 50 mg BID, or 70 mg BID) in patients with CP Ph+ CML whose disease was resistant to or who were intolerant to imatinib. The primary endpoint was to compare MCyR rates between the QD and BID dose schedules after a minimum follow-up of 6 months in patients with imatinib-resistant CP CML. The main secondary efficacy endpoints included comparison of MCyR rates between the two total daily doses (TDD, 100 mg vs 140 mg), rate of complete hematologic response, time to and duration of MCyR, progression free survival (PFS), and overall survival (OS).

Treatment durations in the QD and BID schedules were similar. MCyR rates were comparable between the two schedules, 52% in the QD schedules vs 49% in the BID schedules in patients with imatinib-resistant CML. The difference between the MCyR rates was +2.8% [95% CI: -6.0%; +11.6%], satisfying the Sponsor's pre-specified requirement of $\geq$-15% in the 95% CI lower bound for claiming a non-inferiority of the QD to BID schedule. Comparable efficacy was also observed between the two TDDs. However, there were 4~10% more patients in the 100 mg TDD arms, as compared to those in the 140 mg TDD arms, who required dose escalation for lack of responses. Similar results were also found in patient intolerant to imatinib. The duration of MCyR, PFS, and OS could not be adequately evaluated due to few events observed or detected. Overall, the evidence demonstrated that, in term of MCyR rate, the QD dosing was comparable to the BID dosing and that the 100 mg TDD was comparable to the 140 mg TDD.

The other study in the sNDA is CA180017, a randomized phase 2 study of dasatinib (70 mg BID) vs the high dose of imatinib (400 BID) in patients with CP Ph+ CML whose disease was resistant to prior regular doses (400-600 mg/day) of imatinib. Its primary objective was to estimate MCyR rates at 12 weeks in the two arms. With a minimal follow-up of 12 months, MCyR rate at 12 weeks was 36% in the dasatinib arm compared to 29% in the imatinib arm. With longer follow-up, the overall MCyR rate prior to crossover was 52% in the dasatinib arm compared to 33% in the imatinib arm. Patients who crossed over to the opposite arm after disease progression also had higher MCyR rates with dasatinib treatment (44%) as compared with imatinib treatment (15%). These results suggest that dasatinib may be relatively more active than the high dose imatinib in inducing a MCyR in patients with CP CML who have previously received conventional doses of imatinib but whose disease has progressed.

B. General Approach to Review of the Efficacy of the Drug

Both studies were reviewed in detail for their planned efficacy endpoints. The submitted datasets relevant to efficacy were cross-examined for consistency among datasets and case report forms. Case report forms were checked for subject eligibility, response, and protocol violation and/or deviation, especially for those patients who were suspected to have drug-related death. Several sensitivity analyses were conducted with the help of the statistical reviewer for this sNDA.

C. Detailed Review of Studies

C1: Study CA180034

Indication

A new dose and schedule for dasatinib was proposed for the treatment of patients with CP CML with imatinib resistance or intolerance. There was no new indication associated with this trial.

Protocol Review for CA180034

Study Design

Study CA180034 was an open-label, randomized, multicenter international Phase 3 study designed to evaluate the differences in dasatinib efficacy/safety between two schedules (QD and BID) or two doses (100 mg and 140 mg). The randomization was was stratified on imatinib-resistance vs. imatinib-intolerance. The randomization used a permuted block design with a 1:1:1:1 ratio to assign patients into one of four treatment arms as the 100 mg QD, 140 mg QD, 50 mg BID, and 70 mg BID arm. Therefore, there were two schedules and two doses as follow:

Schedules	QD: (100 mg QD and 140 mg QD) vs BID (50 mg BID and 70 mg BID)
Total daily doses	TDD 100 mg (100 mg QD and 50 mg BID) vs TDD 140 mg TDD (70 mg BID and 140 mg QD)

Objectives

- **Primary**:
  To compare the efficacy of dasatinib when administered QD relative to dasatinib administered BID in the treatment of patients with imatinib-resistant CP CML. The Sponsor proposed that the QD

schedule would be considered efficacious if it could be demonstrated that the true 6-month MCyR rate was not less than 15% of the BID schedule.

- **Secondary**:
  - to estimate the difference of MCyR rates between the two TDD levels (MCyR rate of 100 mg TDD minus MCyR rate of 140 mg TDD) in the imatinib-resistant patients.
  - In the imatinib-resistant patients, to estimate the rate of MCyR and CHR by TDD, schedule and arm, to estimate duration of MCyR and CHR, and to evaluate PFS and OS.
  - In the imatinib-intolerant patients, to assess dasatinib efficacy in MCyR and CHR
  - To evaluate safety differences between the two schedules and two TDDs, particularly on fluid retention, pleural/pericardial effusion, myelosuppression, and dose reduction due to toxicity

Study Centers
There were 139 centers in 31 countries registered for the trial.

Protocol Amendments
There were a total of two amendments to the protocol. Major modifications and other significant protocol events are summarized in Table 3.

Table 3: Protocol Milestones of CA180034

Milestone	Date	Comments
Original Protocol	5/10/2005	
First patient enrolled	7/13/2005	
Amendment #1	3/3/2006	1) Few minor modifications were made to the hematologic response criteria, aligning this phase III trial with the response criteria used in the phase I and II dasatinib trials and the similar criteria used by imatinib clinical trials 2) The restriction of concurrent medications that inhibit platelet function was removed. 3) To state that switching schedules was strictly prohibited
Last patient enrolled	3/26/2006	

Data Cut-off	11/29/2006	
Amendment # 2	3/8/2007	1) to allow subjects on the twice daily dosing schedule to switch to once daily dosing in specific circumstances to optimize the safety of dasatinib.
sNDA submission	5/11/2007	
4-month safety update	9/14/2007	The safety update report was submitted.

Inclusion criteria

- Patients with Ph+ (or BCR/ABL+) CP CML that had either hematologic resistance (primary or acquired) or intolerance to imatinib

  - Definition of Ph+ (or BCR/ABL+) CP CML included all of the followings:
    - < 15% blasts in PB cells or BM
    - < 30% blasts + promyelocytes in PB cells or BM
    - < 20% basophils in PB cells
    - Platelets ≥100,000/mm^3 (or less if related to prior drug therapy)
    - No extra-medullary involvement (except liver or spleen)

  - Resistance to imatinib was defined as either of primary or secondary resistance:

    Primary resistance: Patients whose CML was treated with imatinib showed any of the following:
    - No decrease in WBC count after a ≥ 4-week treatment at the recommended dose of imatinib 400 mg/d or at doses up to 800 mg/d
    - At doses ≥400 mg/d had not achieving a CHR after 3 months
    - At doses ≥400 mg/d had not achieved a MCyR after 6 months
    - At doses ≥400 mg/d have not achieved a CCyR after 12 months

    Acquired resistance: Patients whose CML was treated with imatinib showed any of the following:
    - Achieved MCyR and no longer meet the criteria for MCyR, with a ≥ 30% absolute increase in the percentage of Ph+ metaphases
    - Loss of molecular response concomitant with a ≥ 10% Ph+ metaphases at cytogenetic analysis

- Achieved a MCyR but had evidence of a new mutation in the BCR-ABL domain
- Achieved a confirmed CHR, but no longer met the criteria with WBC counts > 10,000/mm^3 on all assessments over at least a consecutive 2-week period

❖ Intolerance to imatinib was defined as being intolerant to imatinib if patients had a Grade ≥ 3 toxicity considered at least possibly related to imatinib at a dose of ≤ 400 mg/day which led to discontinuation of therapy. Those who tolerated the dose of 400 mg but did not achieve a CCyR and subsequently did not tolerate doses ≥ 600 mg were considered to be resistant to imatinib.

- NO previous history of AP or BP CML
- NO clonal evolution (e.g., trisomy 8, +Ph, iso (17) or trisomy 19) in CP CML
- ECOG PS score 0-2
- Age ≥ 18 years old
- Adequate hepatic and renal function
- Negative pregnancy test in women of childbearing potential who consented to use an adequate method of contraception to avoid pregnancy throughout the study and for a period of at least 1 month before and at least 3 months after the study

Exclusion criteria

Patients with any of the following criteria were excluded from the study.

- Eligible for immediate autologous or allogeneic stem cell transplantation
- A serious uncontrolled medical disorder or active infection that would impair the ability of the subject to receive protocol therapy
- Uncontrolled or significant cardiovascular disease, including:
  - A myocardial infarction within 6 months
  - Uncontrolled angina within 3 months
  - Congestive heart failure within 3 months
  - Diagnosed or suspected congenital long QT syndrome
  - Any history of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or Torsades de Pointe)
  - Prolonged QTcF interval > 450 msec on pre-entry ECG
  - Any history of second or third degree heart block (may be eligible if the patient currently has a pacemaker)
  - Heart rate consistently < 50 beats/minute on pre-entry ECG
  - Uncontrolled hypertension
- History of significant bleeding disorder unrelated to CML [diagnosed congenital bleeding disorder (e.g., von Willebrand's disease), diagnosed acquired bleeding disorder within one year (e.g., acquired anti-factor VIII

antibodies), or clinically significant bleeding from the GI tract within 6 months]

- Concurrent incurable malignancy other than CML
- Evidence of organ dysfunction or digestive dysfunction that would prevent administration of study therapy
- Received the prohibited therapies and/or medicines including any of the following:
  - imatinib mesylate within 7 days
  - interferon or cytarabine within 7 days
  - a targeted small molecule anti-cancer agent within 7 days
  - any other investigational or any antineoplastic agent other than hydroxyurea (HU) within 28 days
- was taking the following drugs that are generally accepted to have a risk of causing Torsades de Pointe, including: quinidine, procainamide, disopyramide, amiodarone, sotalol, ibutilide, dofetilide, erythromycins, clarithromycin, chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide, zyprasidone, cisapride, bepridil, droperidol, methadone, arsenic, chloroquine, domperidone,halofantrine, levomethadyl, sparfloxacin, lidoflazine, pentamidine. For those who had discontinued any of these medications must have a wash-out period of at least 5 days or at least 5 half-lives of the drug (whichever is greater) prior to the first dose of dasatinib.
- Patients taking medications that irreversibly inhibit platelet function (i.e., aspirin, dipyridamole, epoprostenol, eptifibatide, clopidogrel, cilostazol, abciximab, ticlopidine) or anticoagulants [warfarin, heparin/low molecular weight heparin (e.g., danaparoid, dalteparin, tinzaparin, enoxaparin)].

Treatment Plan

Dasatinib was administered orally at a dose of 100 mg or 140 mg QD or 50 mg or 70 mg BID. Patients received their first dose of study therapy within 3 days of randomization. If a scheduled dose was missed or dosing was interrupted for toxicity or for any other reason, these doses were omitted. Patients were treated with dasatinib until disease progression, unacceptable toxicity, withdrawal of subject's consent, or the investigator and the patient felt that it was in the best interest of the patient to discontinue treatment. A dose schedule change from QD to BID was strictly prohibited, however, patients on the twice daily dosing schedule were allowed to switch to once daily dosing in specific circumstances after the second protocol amendment.

Dose Modifications: The levels of dose modification were pre-defined as listed in Table 4. Dose modifications were based on patient's toxicity or response.

Clinical Review Section

Table 4: Levels of Dose Modification (adopted from the Sponsor's protocol)

Dose Level	BID: Dose (mg) every 12 hours		QD: Dose (mg) every 24 hours	
	Arm 1	Arm 2	Arm 3	Arm 4
Escalation (+1)	70	90	140	180
Starting dose	**50**	**70**	**100**	**140**
Reduction (-1)	40	50	80	100
Reduction (-2)	NA	40	NA	80

Dose escalation: Patients could have their dose increased by one dose level in each arm if they had any of the following and no evidence of toxicity:

- No decrease in WBC count after 1 month of uninterrupted dasatinib treatment and/or no CHR after 3 months
- No MCyR after 6 months
- No CCyR after 12 months

Dose reduction and interruption: For non-hematologic drug-related toxicities, dose reduction, interruption, and treatment discontinuation were based on the criteria described in Table 5. Missed doses for any reasons was recommended to be omitted. Additional therapy following a second dose reduction versus treatment discontinuation after a Grade 3 toxicity was at the discretion of the Investigator.

Table 5: Dose Reductions for Dasatinib-Associated Non-Hematologic Toxicity (Based on the Sponsor's)

Toxicity	BMS-354825
Grade 2 adverse event (2nd event) (3rd event)	Decrease current dose by 1 dose level Decrease current dose by one more dose level [a]
Grade 3 adverse event [b] (1st event) (2nd event)	Decrease current dose by 1 dose level Decrease current dose by one more dose level [a]
Grade 3 major adverse event (1st event) (CNS, cardiac, pulmonary [c] or renal)	Decrease current dose by 2 dose levels [a]
Any Grade 4 adverse event (1st event)	Decrease current dose by 2 dose levels [a] or end of treatment
≥ Grade 2 AST, ALT or bilirubin	At the discretion of the Investigator
QTcF > 530 msec	Treatment discontinuation
Any evidence of bleeding [d]	At the discretion of the Investigator

[a] In subjects randomized to arm 2 or 4 only.
Discontinuation for further episodes is left at Investigator's decision in the best interest of the subject.

[b] Despite adequate/maximal medical intervention and/or prophylaxis

[c] Pleural effusion is not included in pulmonary toxicity.

[d] No dose reduction during an episode of severe thrombopenia.

For hematologic toxicity, dose reduction managements were basically consistent with the current dasatinib label and are summarized in Table 6.

Table 6: Dose Reduction and Interruption for Hematologic Toxicity (Summarized based on the protocol)

Subject Status	Dose Interruption	Dose Reduction
Febrile Neutropenia (Fever ≥ 38.5°C and ANC < 1,000/mm^3)	Interrupted until ANC<Grade 3 and T<38.0)	Reduce one dose level at re-initiation. For a recurrent episode in patients in Arm 2 or 4, a second dose reduction could be done.
Grade 3/ 4 non-febrile Neutropenia	Interrupted until ANC < Grade 3.	Resume at full dose if recovery within 7 days; one dose level reduction if recovery occurred > 7 days. For a second episode with a recovery > 7 days, a second dose reduction could be done for patients in Arm 2 or 4.
Grade 4 thrombocytopenia within the first 2 months of treatment	Interrupted until recovery to Grade ≤ 2	Restarted at full dose. For a second episode, one dose level reduction. For a third episode in Arm 2 or 4, a second reduction could be done.
Grade 3 or 4 thrombocytopenia after > 3 months of treatment	Interrupted until recovery to Grade ≤ 2	Resumed with one dose level reduction

Treatment discontinuation: Treatment discontinuation was advised for any of the following reasons:

- Voluntarily withdrawn
- Any clinical adverse reaction, laboratory abnormality or inter-current illness which, in the opinion of the Investigator, indicated that continued treatment with study therapy was not in the best interest of the patient
- QTcF value of > 530 msec
- Disease progression at the highest tolerated dose
- Decision to undergo stem cell transplantation
- Pregnancy
- Termination of the study by the Sponsor for safety reasons
- Imprisonment or the compulsory detention for treatment of either a psychiatric or physical (e.g., infectious disease)

Concurrent Treatment

No other therapy for the treatment of CML with the exception of hydroxyurea for WBC > 50,000/mm^3, was permitted while the subject was

on-study. Colony-stimulating factors (e.g., G-CSF, GM-CSF, etc) and erythropoietin were permitted at the discretion of the Investigator.

Medications associated with QT interval prolongation were prohibited in this study, which are as listed in the section of Exclusion Criteria.

Antacid drugs such as H2-blockers (eg. Ranitidine) or proton pump inhibitors (eg. omeprazole) were restricted as they could significantly reduce bioavailability of dasatinib.

Efficacy Assessments

1) Primary Endpoint

The primary efficacy endpoint of CA180034 was the comparison of the rate of 6-month major cytogenetic response (MCyR) by schedule and dose. The cytogenetic response (CyR) was evaluated with bone marrow biopsies or aspirates. Evaluation of the CyR using HM-FISH or PCR only was not accepted.

CyR was based on the prevalence of Ph+ metaphases among cells in metaphase on a bone marrow sample, which was obtained after 3 and 6 months of treatment and then every 6 months. Ideally, 25 metaphases but at least 20 metaphases from a bone marrow sample should be evaluated.

Definition of Cytogenetic Response

The criteria for CyR were 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

MCyR was defined as CCyR **or** PCyR. Best CyR was defined as the best response obtained at any time during the study.

2) Secondary Endpoints

Secondary efficacy endpoints included the rate of CHR, duration of MCyR and CHR, PFS, and OS.

Hematologic response was determined by CBC, differential and PLT count, which were performed within 72 hours prior to start of study therapy, at least every 2 weeks for the first 12 weeks, then every 3 months for 2 years, every 6 months after 2 years, and at the end of treatment visit.

Definition of Complete Hematologic Response
A Complete Hematologic Response (CHR) was established when all of the following criteria were met:

- WBC $\leq$ institutional upper limit of normal
- Platelets $\leq$ 450,000/mm^3
- No blasts or promyelocytes in peripheral blood
- < 5% myelocytes plus metamyelocytes in peripheral blood
- peripheral blood basophils < 20%
- No extra-medullary involvement including no splenomegaly or hepatomegaly

A confirmed CHR (cCHR) was obtained when all above criteria were maintained for at least 28 days after they were first met.

The duration of MCyR was measured from the first day all criteria were met for CCyR or PCyR until the date of disease progression or death. Patients who neither progressed nor died were censored on the date of their last cytogenetic assessment. The duration of CHR was assessed similarly as for the duration of MCyR.

Progression-free survival was defined as the time from randomization until the time of progressive disease was first documented. Patients who died without a reported prior progression were considered to have a disease progression on the date of their death. Patients who did not progress nor die were censored on the date of their last assessment.

Progressive Disease was defined with any of the following criteria. The date of progression was defined as the date any of the criteria was first met.

- Achieved a CHR and subsequently no longer meet the criteria consistently over a consecutive 2-week period after starting their maximum dose of dasatinib
- Had no CHR after receiving their maximum dose and had an increase in WBC count defined as a doubling of the count from the lowest value to > 20,000/mm^3 or an increase by > 50,000/mm^3 on two assessments performed at least 2 weeks apart

- Met the criteria of AP or BP CML at any time
- Had a MCyR and subsequently no longer met the criteria for MCyR after starting their maximum dose
- Had a ≥ 30% absolute increase in the number of Ph+ metaphases.

Overall survival time was defined as the time from randomization until the time of death. Patients who were lost to follow-up were censored on the last date the subject was known to be alive.

Statistical Methods

All efficacy analyses were planned to be performed in randomized patients unless otherwise specified. Evaluations would be done by schedule, total daily dose, and arm assignment for the imatinib-resistant patients.

The primary efficacy endpoint was to estimate the difference of 6-month MCyR rates between the QD and BID schedules in the imatinib-resistant patients. The Sponsor pre-specified that if the lower bound of the asymptotic 95% CI of the difference (the MCyR rate of the QD schedule – that of the BID schedule) is ≥ -15%, non-inferiority of the QD schedule relative to the BID schedule would be deduced. If the lower bound of the asymptotic 95% CI of the difference lies above zero, superiority of the QD schedule relative to the BID schedule would be claimed.

The main secondary analysis was to estimate the difference of MCyR rates between the two total daily doses (the 100 mg TDD MCyR rate minus the 140 mg TDD MCyR rate) in the imatinib-resistant patients. A modified Gail and Simon method for non-inferiority would be used to test for a qualitative interaction between TDD levels and schedules.

Other secondary efficacy analyses in the imatinib-resistant subjects included the rate of CHR along with its asymptotic two-sided 95% CI, time to, and duration of MCyR and CHR, PFS, and OS. The duration of MCyR and CHR, PFS and OS was to be estimated via the Kaplan-Meier product-limit method.

Efficacy analyses (MCyR and CHR) also were planned for the imatinib-intolerant patients.

Reviewer's Comments
The primary endpoint, MCyR rates at 6 months, used for comparison of the efficacy of four different dose-schedules in CA180034 appears to be adequate, since the initial accelerated approval of dasatinib was also based on cytogenetic and hematologic response rates in patients who have received imatinib.

RESULTS

Study Conduct

There were 139 centers worldwide in 31 countries that enrolled a total of 724 patients for CA180034. Of those enrolled, 670 patients in 136 study centers were randomized 1:1:1:1 to one of the four dose schedules. After randomization, 662 patients were treated with dasatinib at their assigned dose schedules. Ninety percent of these randomized patients were from 18 countries. The country distribution of the randomizations with ≥10 patients is shown in Table 7, along with the number of study centers.

Table 7: Country Distribution of Number of Patients and Study Centers in CA180034

Country	Number of Randomized Patients (%)	Number of Study Centers Involved
USA	205 (30.6%)	37
FRANCE	66 (10.0%)	11
KOREA	45 (6.7%)	4
GERMANY	42 (6.3%)	6
BRAZIL	40 (6.0%)	5
ARGENTINA	30 (4.5%)	4
UK	25 (3.7%)	6
BELGIUM	19 (2.8%)	6
ITALY	19 (2.8%)	7
AUSTRAILIA	18 (2.7%)	6
DENMARK	16 (2.4%)	3
POLAND	16 (2.4%)	6
RUSSIA	16 (2.4)	2
CANADA	14 (2.1%)	3
MEXICO	11 (1.6%)	1
SWITZERLAND	11 (1.6%)	1
IRELAND	10 (1.5%)	2
SWEDEN	10 (1.5%)	2

Ninety percent of these randomized patients were from 18 countries. The other 11 countries only had 9% of the study patients. The top country enrollment for the study was in the USA, where 205 (30%) of the study patients were randomized in 37 study centers. On the other hand, as shown in Table 8, ninety three (70%) of the 136 centers have ≤ 5 patients enrolled, with 34% (233/670) of the total enrollments; whereas fifteen

(11%) centers with enrolling sizes of 11~25 had 34% (230/670) of the total.

Table 8: Distribution of Study Sites and Number of Patients by Enrollment Category in CA180034

Size of Enrollment per site	Number of Sites/per Category	Total Number of Patients /per Category (% of total)
1~5 Subjects	93	233 (35%)
6~10 Subjects	28	207 (31%)
11~20 Subjects	12	159 (24%)
21~25 Subjects	3*	71 (10%)

*The three top enrollment centers were in Korea, US, and France.

All patients were consented prior to initiation of treatment.

Reviewer Comments: *The enrolled subjects of the study are geographically heterogeneous. This fact suggests that the results of the study may be generalized.*

Protocol Violations and Deviations

There were about 6.6% of patients found to have either significant protocol violations or deviations or both, which are classified in Table 9. Their study identification numbers are listed in Table 10. The commonest minor deviation was no CBC or Chem20 tests performed within 72 hours of dosing, which would less likely impact the primary endpoint evaluation. Some patients who did not have treatment after randomization are shown in Table 11.

Table 9: Summary of Significant Protocol Violations and/or Deviations of CA180034

PROTOCOL DEVIATION/ VIOLATION	100 mg qd (N=167)	140 mg qd (N=167)	50 mg bid (N=168)	70 mg bid (N=168)
Ph+/BCR-ABL or CP CML Criteria Unmet	4	0	1	2
Eligibility Criteria Unmet	2	4	2	4
Switched Dose Schedule (QD->BID or BID->QD)	2	2	4	0
Received Prohibited Therapies*	1	2	7	7
TOTAL	9	8	14	13

*Received interferon or cytarabine within 7 days of dosing or antineoplastic agent or investigational drug within 28 days of dosing

Table 10: Patients with Eligibility Violations in CA180034

	100 mg qd (N=167)	140 mg qd (N=167)	50 mg bid (N=168)	70 mg bid (N=168)
ID of Patients with Eligibility Violation **(*Imatinib-resistant; # imatinib-intolerance)**	*CA180034-125-34383 #CA180034-140-34028 #CA180034-183-34529 *CA180034-209-34376 *CA180034-210-34179 #CA180034-69-34664	*CA180034-45-34552 *CA180034-6-34265 CA180034-90-34686 CA180034-94-34004	*CA180034-189-34092 *CA180034-6-34127 #CA180034-69-34665	*CA180034-128-34461 *CA180034-136-34613 *CA180034-149-34416 *CA180034-214-34497 *CA180034-32-34507 *CA180034-90-34187

Table 11: Patients without Treatment after Randomization in CA180034

	100 mg qd (N=167)	140 mg qd (N=167)	50 mg bid (N=168)	70 mg bid (N=168)
ID of Patients with no Treatment **(*Imatinib-resistant; # imatinib-intolerance)**	*CA180034-32-34044	*CA180034-10-34501 *CA180034-55-34711 *CA180034-57-34334 *CA180034-97-34030	*CA180034-140-34023 #CA180034-62-34213	*CA180034-145-34615

Reviewer's Comments: *In the arms of 50 mg BID or 70 mg BID, there were more patients who received other CML-effective treatments within 7 or 28 days of dasatinib start. The impacts of such treatments on the primary endpoint could be ignored for the first bone marrow sampling was not done until 3 months after dasatinib treatment. Otherwise, the major protocol violations/deviations were distributed similarly among the four dose schedules.*

Characteristics of studied subjects

Clinical Review Section

Both baseline and disease characteristics of the randomized patients were reviewed and analyzed with the datasets provided by the sponsor. The information collected in that dataset was randomly checked against that shown in CRFs. They were consistent. Those characteristics are summarized in Table 12.

Table 12: Baseline and Disease Characteristics of the CA180034 Patients

	100mg QD (N=167)	140 mg QD (n=167)	50 mg BID (n=168)	70 mg BID (n=168)
Age, median (Range)	56 (20-78)	54 (20-84)	55 (21-84)	54 (18-83)
Gender (%)				
Male	50%	42%	51%	46%
Female	50%	58%	49%	54%
ECOG PS 0-1 (%)	98%	99%	98%	98%
Median CML duration (month) (range)	55 (2–250)	56 (1–227)	51 (4–212)	53 (1–246)
Imatinib Status (%)				
Resistant	74%	74%	74%	76%
Intolerant	26%	24%	24%	24%
Prior Imatinib Therapy				
400-600 mg/day (%)	64%	67%	67%	66%
>600 mg/day (%)	37%	33%	33%	33%
Length of Prior Imatinib Therapy				
≤ 3 years	54%	59%	64%	58%
> 3 years	46%	41%	36%	42%
Prior Best Cytogenetic Response to Imatinib				
MCyR	46%	42%	39%	42%
Cytotoxic chemotherapy	23%	25%	31%	26%
Interferon	52%	56%	52%	49%
Stem cell transplant	6%	3%	8%	4%

Reviewer Comments: *All of the listed characteristics or factors are basically balanced among the four treatments arms, especially prior treatments with imatinib.*

Efficacy Results

The primary efficacy endpoint of CA180034 was to compare the MCyR rates of dasatinib after a minimum follow-up of 6 months when administered QD relative to dasatinib administered BID in the treatment of patients with CP CML resistant to imatinib. The Sponsor's pre-specified lower bound of the 95% CI for the difference in MCyR rate was $\geq$ -15% for deducing a non-inferiority of the QD schedule relative to the BID schedule. Similar criteria were also used for evaluating some of the secondary endpoints, comparing the differences in MCyR rate between the 100 mg TDD and 140 mg TDD dose groups in patients with CML with resistance or intolerance to imatinb, or between the QD and BID dose schedules in patients intolerant to imatinib. Other secondary endpoints included evaluating the rate of CHR, duration of MCyR, progression free survival, and overall survival.

The overall MCyR and CHR in all randomized patients are summarized per dose schedule in Table 13. The MCyR rates were comparable in all dose schedules.

Table 13: Major Cytogenetic and Hematologic Responses in Randomized Patients in CA180034 (FDA adjudicated)

Response (%)	100 mg QD (N=167)	140 mg QD (N=167)	50 mg BID (N=168)	70 mg BID (N=168)
MCyR				
All Patients	98 (59%)	93 (56%)	90 (54%)	93 (55%)
Imatinib-Resistant	66/124 (53%)	62/123 (50%)	58/124 (47%)	65/127 (51%)
Imatinib-Intolerant	32/43 (74%)	31/44 (70%)	32/44 (73%)	28/41 (61%)
CCyR				
All Patients	69 (41%)	74 (44%)	70 (42%)	75 (45%)
Imatinib-Resistant	42/124 (34%)	44/123 (36%)	43/124 (35%)	50/127 (39%)
Imatinib-Intolerant	27/43 (63%)	30/44 (68%)	27/44 (61%)	25/41 (61%)
CHR				
All Patients	150 (90%)	143 (86%)	154 (92%)	146 (87%)
Imatinib-Resistant	107/124 (86%)	105/123 (85%)	113/125 (91%)	111/127 (87%)
Imatinib-Intolerant	43/43 (100%)	38/44 (86%)	41/44 (93%)	35/41 (85%)

Reviewer's Comments:
Both MCyR and CHR rates, as shown in the table above, appear to be comparable across all the treatment arms in either patient with imatinib-resistant CP CML or patients with the disease who were intolerant to imatinib.

The primary endpoint was evaluated in the randomized patients with CP CML resistant to imatinib. The difference in MCyR rate between the QD and BID schedules, as shown in Table 14, was +2.8%, whose lower bound of the 95% CI was -6.0%. According to the Sponsor, this difference was larger than the pre-specified $\geq$ -15% for deducing a non-inferiority of the QD schedule as compared to the BID schedule.

Table 14: Major Cytogenetic Responses in Patients with Imatinib-Resistant Disease By Schedule in CA180034 (FDA adjudicated)

	QD Dosing (N=247)	BID Dosing (N=251)
MCyR (%) **95% CI**	128 (51.8%) (45.4-58.2%)	123 (49%) (42.7-55.4%)
Difference of MCyR Rate **95% CI**	2.8% -6.0%; 11.6%	

To examine the reliability of the difference between the QD and BID dose schedules, a sensitivity analysis was performed with exclusion of the imatinib-resistant patients who had significant violations in eligibility criteria, as shown in Table 10, and who had no treatment after randomization, as shown in Table 11. There were a total of 10 patients in each schedule excluded for this sensitivity analysis, of which one patient (CA180034-125-34383) in the QD schedules and four patients (CA180034-6-34127, CA180034-128-34461, CA180034-32-34507, and CA180034-90-34187) in the BID schedules had a MCyR. The results of the analysis are shown in Table 15. The difference between the two dose schedules appears to be similar to the initial results. Its lower 95% CI bound is -4.7%, greater than the Sponsor's pre-specified allowance of -15%.

Table 15: Sensitivity Analysis with Exclusion of Patients with Imatinib-Resistant Disease With Significant Violations in Eligibility Criteria And With No Treatment in CA180034

	QD Dosing (N=237)	BID Dosing (N=241)
MCyR (%) **95% CI**	127 (53.6%) (47.0%-60.0%)	119 (49.4%) (42.9%-55.9%)
Difference of MCyR Rate **95% CI**	4.2% (-4.7%; 13.2%)	

The effects of the two different daily doses, 100 mg TDD vs 140 mg TDD were also evaluated for their difference in MCyR rate in patients with imatinib-resistant disease. As shown in Table 16, the response rates were similar between the two TTD groups, with a difference of -0.8%. The lower bound of 95% CI of the difference is greater than -15%, suggestive of the comparability of the 100 mg TDD to the 140 mg TDD in attaining a MCyR rate.

Table 16: Major Cytogenetic Responses in Patients with Imatinib-Resistant Disease By Total Daily Dose in CA180034 (FDA adjudicated)

	100 mg TDD (N=248)	**140 mg TDD (N=250)**
MCyR (%) **95% CI**	124 (50.0%) (43.6%-58.2%)	127 (50.8%) (44.4-57.2%)
Difference of MCyR Rate **95% CI**	-0.8% -9.6%; 8.0%	

Since the two studied different schedules or daily doses generated similar MCyR rates in their respective, one can reason that the proposed new dose schdule100 mg QD would meet the Sponsor's non-inferiority test used for the study when compared to the previously recommended dose schedule, 70 mg BID. To test this hypothesis, a sensitivity analysis was performed and the results are shown in Table 17.

Table 17: Major Cytogenetic Responses in Patients with Imatinib-Resistant Disease Between the Proposed New and the Previously Recommended Dose Schedules in CA180034

	100 mg QD Dosing (N=124)	**70 mg BID Dosing (N=127)**
MCyR (%) **95% CI**	66 (53.2%) (44.0%-62.2%)	65 (51.2%) (42.2%-60.2%)
Difference of MCyR Rate **95% CI**	2.0% (-10.3%; 14.4%)	

Reviewer's Comments:

The MCyR rates between the two schedules, two doses, and the two individual 100 mg QD and 70 mg BID dose schedules are comparable and their differences sustain the Sponsor's pre-specified non-inferiority test. Although there had not been a consensus about the selected fixed 95% CI margin allowance for claiming a non-inferiority in comparing different dose

schedules, the current lower bound used in this study appears to be clinically acceptable for the purpose of optimizing benefit/risk ratio of dasatinib. With the sensitivity analyses as shown above, the new dose schedule 100 mg QD is comparable in attaining a MCyR rate to the previously recommended dose schedule 70 mg BID.

Furthermore, the reviewer and statistical reviewer evaluated MCyR rates in all patients based on gender and age groups and the results are shown in Table 18.

Table 18: MCyR and MCyR Rate by Gender and Age in CA180034

Subgroup	Category	100 mg QD N = 167	140 mg QD N = 167	50 mg BID N = 168	70 mg BID N = 168
Age	< 65	73 / 116 (62.9%)	79 / 127 (62.2%)	71 / 128 (55.5%)	71 / 120 (59.2%)
	≥ 65	25 / 51 (49.0%)	14 / 40 (35.0%)	19 / 40 (47.5%)	22 / 48 (45.8%)
Gender	Female	47 / 83 (56.6%)	56 / 97 (57.7%)	44 / 83 (53.0%)	48 / 91 (52.8%)
	Male	51 / 84 (60.7%)	37 / 70 (52.9%)	46 / 85 (54.1%)	45 / 77 (58.4%)

The duration of MCyR in patients with imatinib-resistant disease who had achieved MCyR appeared to be similar between the schedules and doses, which are shown in Table 19. However, few events of progression were observed with a short time of follow-up. Similar issues were encountered in evaluating PFS and OS. The current data are not adequate to assess those secondary endpoints.

Table 19: Duration of Major Cytogenetic Response in Patients with Imatinib-Resistant Disease in CA180034

	100 mg QD (N=167)	140 mg QD (N=167)	50 mg BID (N=168)	70 mg BID (N=168)
# of MCyR Responder /Imatinib-Resistant Patients	66/124	62/123	58/124	65/127
# of McyR Progression	0	3	0	3

The CHR rates were also similar in the four dose schedules in patients with imatinib-resistant CML, which are shown in Table 20. The rates are comparable between the two schedules or two daily doses.

Table 20: Complete Hematologic Response in Patient with Imatinib-Resistant Disease in CA180034 (FDA adjudicated)

	100 mg QD (N=167)	140 mg QD (N=167)	50 mg BID (N=168)	70 mg BID (N=168)
CHR / Imatinib-Resistant Patients **(%)**	107/124 (86%)	105/123 (85%)	113/124 (91%)	111/127 (87%)
CHR (%)	QD: 212/247(86%)		BID: 224/251 (89%)	
CHR (%)	100 mg TDD: 220/248 (89%) 140 mg TDD: 216/250 (86%)			

For patients with CP CML who were intolerant to imatinib, which were counted about 25% in each randomized arm, their overall MCyR rates, as shown in Table 21, were also similar across each arm. Comparing the MCyR rates between the QD and BID schedules or the 100 mg and 140 daily doses, as shown in Table 22, the differences were 1.8% for the two schedules, 4.2% for the two doses, with the lower bounds of 95% CI of the differences greater than $\geq$-15%. These results suggested that the MCyRs between QD and BID schedules or between 100 mg and 140 mg TDD were comparable in imatinib-intolerant patients.

Table 21: Major Cytogenetic Response in the Imatinib-Intolerant Patients in CA180034 (FDA adjudicated)

Response (%)	100 mg QD (N=167)	140 mg QD (N=167)	50 mg BID (N=168)	70 mg BID (N=168)
MCyR /Imatinib-Intolerant	32/43 (74%)	31/44 (70%)	32/44 (73%)	28/41 (68%)
CCyR / Imatinib-Intolerant	27/43 (63)	30/44 (68%)	27/44 (61%)	25/41 (61%)

Table 22: Major Cytogenetic Responses in Patients with Imatinib-Intolerance By Schedule and Total Daily Dose in CA180034

	Schedule		Total Daily Dose	
	QD Dosing (N=87)	BID Dosing (N=85)	100 mg TDD (N=87)	140 mg TDD (N=85)
MCyR (%) 95% CI	63 (72.4%) (61.8%-81.5%)	60 (70.6%) (59.7%-80.0%%)	64 (73.6%) (63.0%-82.4%)	59 (69.4%) (58.5%-79.0%)
Difference of MCyR Rate (95% CI)	1.8% (-11.7%; 15.3%)		4.2% (-9.3%; 17.6%)	

The CHR rates in patients with CP CML who were intolerant to imatinib were also similar in the two schedules and two daily doses, which are shown in Table 23.

Table 23: Complete Hematologic Response in the Imaitinib-Intolerant Patients in CA180034 (FDA adjudicated)

	100 mg QD (N=167)	**140 mg QD (N=167)**	**50 mg BID (N=168)**	**70 mg BID (N=168)**
CHR/Imatinib-Intolerant **(%)**	43/43 (100%)	38/44 (86%)	41/44 (93%)	35/41 (85%)
CHR (%)	QD: 81/87 (93%)		BID: 76/85 (89%)	
CHR (%)	100 mg TDD: 84/87 (97%) 140 mg TDD: 73/85 (86%)			

Taken together, the two studied schedules (QD vs BID) and two daily doses (100 mg vs 140 mg) of dasatinib appear to have comparable treatment efficacy as assessed with the rates of MCyR and CHR in patients with CP CML resistant to and who are intolerant to imatinib.

Study CA180017

Indication

Proposed to compare the effectiveness of dasatinib vs a high dose of imatinib in CP CML patients resistant to the conventional doses of imatinib.

Protocol Review for CA180017

Study Design

This was a randomized open label Phase 2 study of dasatinib (70 mg BID) versus imatinib (400 mg BID) in patients with chronic phase Ph+ CML who have had resistance while being treated with a dose of imatinib of 400 to 600 mg daily. Randomization was stratified by study site and by cytogenetic response on imatinib, and was in a 2:1 ratio to dasatinib vs imatinib. Its primary objective was to compare the 12-week MCyR rates of dasatinib vs imatinib. A minimum of 150 subjects was estimated to complete this study. Patients were allowed to cross over to the opposite arm after disease progression or intolerance to their initially assigned treatment.

Objectives

- **Primary**:
  To estimate major cytogenetic response rates of dasatinib and imatinib at 800 mg daily at 12 weeks in subjects with chronic phase Ph+ CML who have disease that is resistant to imatinib.

- **Secondary**:

  - To estimate MCyR at any time (prior to crossover) in both treatment arms
  - To assess the durability of major cytogenetic response and time to MCyR prior to crossover in both treatment arms
  - To estimate complete hematologic response (CHR) rate prior to crossover in both treatment arms.
  - To assess the durability of CHR and time to CHR prior to crossover in both treatment arms
  - To estimate major molecular response rates by measuring BCR-ABL transcripts in blood during treatment using quantitative RT-PCR prior to crossover
  - To estimate post-crossover efficacy endpoints in subjects who cross over
  - To assess the health-related quality of life in both treatment arms prior to crossover using the FACT-G
  - To assess further the safety and tolerability of dasatinib
  - To collect blood samples for pharmacokinetic analysis of dasatinib given BID that will contribute to population pharmacokinetic modeling.

Study Centers
There were approximately 65 centers worldwide planned for the trial.

Protocol Amendments
There were a total of two amendments to the protocol. Major modifications and other significant protocol events are summarized in Table 24.

Table 24: Protocol milestones of CA180017

Milestone	Date	Comments
Original Protocol	11/18/2004	
First patient enrolled	2/10/2005	
Amendment #1	4/28/2005	To rescind the permission to use anagrelide.

Amendment #2	7/14/2005	To keep basophilis < 20% in response criteria.
Last patient enrolled	9/21/2005	
Data cut-off	11/25/2006	
sNDA submission	5/11/2007	

Inclusion criteria

- Patients with Ph+ CP CML that had either hematologic or cytogenetic resistance to imatinib
- Has not previously been treated with imatinib at a dose greater than 600 mg/day
- Developed resistance to disease while receiving an imatinib dose 400 – 600 mg/day.
- Able to tolerate chronic administration of imatinib at the highest dose the subject has received in the past with no Grade 3 or greater non-hematologic toxicity related to imatinib or Grade 4 hematologic toxicity that is imatinib-related lasting more than 7 days
- No previous history of AP or BP CML
- ECOG PS score 0-2
- Age $\geq$ 18 years old
- Adequate hepatic and renal function
- Negative pregnancy test in women of childbearing potential who consented to use an adequate method of contraception to avoid pregnancy throughout the study and for a period of at least 1 month before and at least 3 months after the study

Exclusion criteria

Patients with any of the following criteria were excluded from the study.

- Prior therapy with dasatinib
- Prior treatment with imatinib at a dose > 600 mg daily
- With known BCR-ABL mutation including L248V, G250E, Q252H/R, Y253H/F, E255K/V, T315I/D, F317L, H369P/R
- Intolerance to imatinib at any dose.
- Have received imatinib within 7 days
- Eligible and willing to undergo transplantation during the screening
- A serious uncontrolled medical disorder or active infection that would impair the ability of the subject to receive protocol therapy
- Uncontrolled or significant cardiovascular disease, including:
  - A myocardial infarction within 6 months
  - Uncontrolled angina within 3 months

- Congestive heart failure within 3 months
- Diagnosed or suspected congenital long QT syndrome
- Any history of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or Torsades de Pointe)
- Prolonged QTcF interval > 450 msec on pre-entry ECG
- Any history of second or third degree heart block (may be eligible if the patient currently has a pacemaker)
- Heart rate consistently < 50 beats/minute on pre-entry ECG

- Uncontrolled hypertension
- History of significant bleeding disorder unrelated to CML
- Have received interferon or cytarabine within 14 days or a targeted small molecule anti-cancer agent within 14 days, any other investigational or antineoplastic agent within 28 days prior to study start
- Taking drugs that are generally accepted to have a risk of causing Torsade de Pointes or known to be potent CYP3A4 inhibitors (i.e. Ketoconazole, ritonavir) or inducers (i.e. rifampin, efavirenz).

Reviewer's Comments:

The definitions of CP CML and resistance to imatinib as well as imatinib intolerance were same as that described in Study 180034. The list of medications in Exclusion Criteria was same as that mentioned for study 180034.

Treatment Plan

Dasatinib was administered orally at a dose of 70 mg twice daily. Patients should take drug approximately every 12 hours. Patients were treated with dasatinib until disease progression, unacceptable toxicity, withdrawal of subject's consent, or the investigator and the patient felt that it was in the best interest of the patient to discontinue treatment. Patients with progression or failure to achieve MCyR after 12 weeks at 70 mg BID would be escalated to 90 mg BID. Patients were allowed to cross over to imatinib treatment after disease progression, with a 2 day wash-out period. If a scheduled dose was missed or dosing was interrupted for toxicity or for any other reason, these doses were omitted.

Patients randomized to imatinib arm were treated with imatinib at a total oral dose of 800 mg daily, administered as 400 mg BID. Patients continued treatment until disease progression or adverse events that by protocol definition or investigator opinion would preclude additional imatinib treatment. Patients were then crossed over to dasatinib following a one-week wash-out period. Missed imatinib doses for any reasons were omitted.

Dose escalation of imatinib was prohibited. However, one dose reduction to 600 mg/day was allowed if the patient had not previously been treated at that dose level.

Dose Modifications:
Dose modification guidelines for dasatinib were similar to that described in study CA180034.

For imatinib: if a severe non-hematologic adverse reaction developed (such as severe hepatotoxicity or severe fluid retention), it should have been withheld until the event was resolved. For Grade 3 non-hematologic adverse events at least possibly related to imatinib, imatinib should not have been resumed. For imatinib-related hematologic toxicities, dosing was guided based on the criteria derived from imatinib label, as shown in Table 6. In principal, if a patient had not previously received imatinib at a dose of 600 mg/d, its dose might be reduced to 600 mg/day. However, if prior imatinib resistance occurred at a dose of 600 mg/day, patients with intolerable toxicity at 800 mg were recommended to receive dasatinib.

Treatment discontinuation:
Treatments with the study drugs had to be discontinued with any of the following:

- Withdrawal of informed consent
- Any clinical adverse event, laboratory abnormality or intercurrent illness suggesting that continued treatment with study therapy was not in the best interest of the patient
- Disease progression
- Pregnancy

Efficacy Assessments

1) Primary Endpoint

The primary efficacy endpoint of CA180017 was to evaluate MCyR rate at 12 weeks in each treatment arm, defined as the proportion of all randomized patients with best response of CCyR or PCyR at the 12 weeks measurement. If cytogenetic assessment was not performed prior to crossover, patients would be considered as non-responders.

2) Secondary Endpoints

Secondary efficacy endpoints included the MCyR rates at any time, the rate of CHR, duration of MCyR and CHR, major molecular response, PFS, and OS. Safety evaluation was another endpoint that was assessed continuously.

Reviewer's Comments:
The definitions of cytogenetic and hematologic responses as well as disease progression were basically same as that described in study CA180034.

Statistical Methods

All efficacy analyses were planned to be performed in randomized patients. For the primary endpoint, MCyR rates would be calculated for each arm as randomized. A two-sided 95% exact confidence interval would be computed for the MCyR rate using the Clopper-Pearson method in each treatment arm. For the secondary endpoints, the duration of major cytogenetic response would be estimated via the Kaplan-Meier product-limit method. A two-sided, 95% confidence interval for median duration of major cytogenetic response would be computed using the method of Brookmeyer and Crowley. A two-sided Clopper-Pearson 95% exact confidence interval would be calculated for the CHR rates and for the major molecular response rates.

In addition, analyses of the efficacy variables after cross over would also be performed on the dataset of patients who crossed-over to dasatinib and on the dataset of patients who crossed-over to imatinib. No comparison between the two treatment arms was planned.

RESULTS

Study Conduct

There were 53 study sites in 22 countries involved in the treatment of 150 patients randomized in the study. Eleven centers had 49% of the total. The rest of patients were in other 42 study centers with an enrollment of $\leq$ 4 patients. In term of country distribution, a total 63% (94/150) of the enrollments were in Poland (27), Brazil (24), Russia (17), France (16), and USA (10). All the patients were consented for their participation.

Protocol Violations and Deviations

The significant violations and deviations that may have impacted on the analysis of efficacy are summarized in Table 25. The commonest minor deviation observed in 97% of the studied patients was no general lab tests performed within 72 hours of dosing.

Table 25: CA180017 Patients with Major Violations or Deviations that May Affect Efficacy Assessment

Violation or Deviation	Dasatinib (N=101)		Imatinib (N=49)	
	Sum N (%)	Subject ID	Sum N (%)	Subject ID
Resistance or CP CML Criteria Unmet	6 (6%)	CA180017-2-17107* CA180017-19-17011* CA180017-44-17002* CA180017-69-17020 CA180017-100-17028* CA180017-172-17058	2 (4%)	CA180017-102-17114 CA180017-140-17143
Efficacy Assessment not performed as scheduled	5 (5%)	CA180017-19-17011 CA180017-61-17138 CA180017-90-17065 CA180017-100-17029 CA180017-135-17132	0	

*Patients with a MCyR at baseline and not meeting imatinib resistance.

Characteristics of studied patients in CA180017

The characteristics of the patients in this study are listed in Table 26.

Table 26: Baseline and Disease Characteristics of the CA180017 Patients

	Dasatinib 70 mg BID (N=101)	Imatinib 400 mg BID (N=49)
Age, median (Range)	51 (24-85)	51 (24-80)
Gender (%) Male Female	53% 48%	45% 55%
ECOG PS 0-1 (%)	97%	97%
Median CML duration (month) (range)	64 (6–166)	52 (14–133)
Prior Imatinib Therapy 400-600 mg/day (%) >600 mg/day (%)	 99% 1%	 100% 0%
Length of Prior Imatinib Therapy ≤ 3 years > 3 years	 55% 45%	 69% 31%
Prior Best Cytogenetic Response to Imatinib MCyR	38%	29%
Cytotoxic chemotherapy	39%	37%
Interferon	73%	67%
Stem cell transplant	7%	4%

Reviewer's Comments: *As compared to the imatinib arm, there are 7% more patients in the dasatinib arm who had major protocol violations and deviations. The effects of that difference will be examined in a sensitivity analysis described in next section. The baseline and disease characteristics are basically balanced between the two treatment arms.*

Efficacy Results

The primary objective of CA180017 was to estimate MCyR rates at 12 weeks in patients with imatinib-resistant CP CML treated with dasatinib 70 mg BID vs imatinib 400 mg BID. Main secondary objectives included MCyR at any time prior to cross-over, duration of MCyR, and PFS.

All randomized patients were treated. The median treatment duration was 13.7 months (0.2~19.3 months) for the dasatinib arm, 3.1 months (0.2~ 15.6 months) for the imatinib arm. The MCyR rates at 12 weeks and at any time prior to cross-over were summarized in Table 27. The CHR rates at 12 weeks were comparable, 93% in the dasatinib arm and 82% in the imatinib arm, respectively.

Table 27: MCyR rates at 12 weeks in CA180017

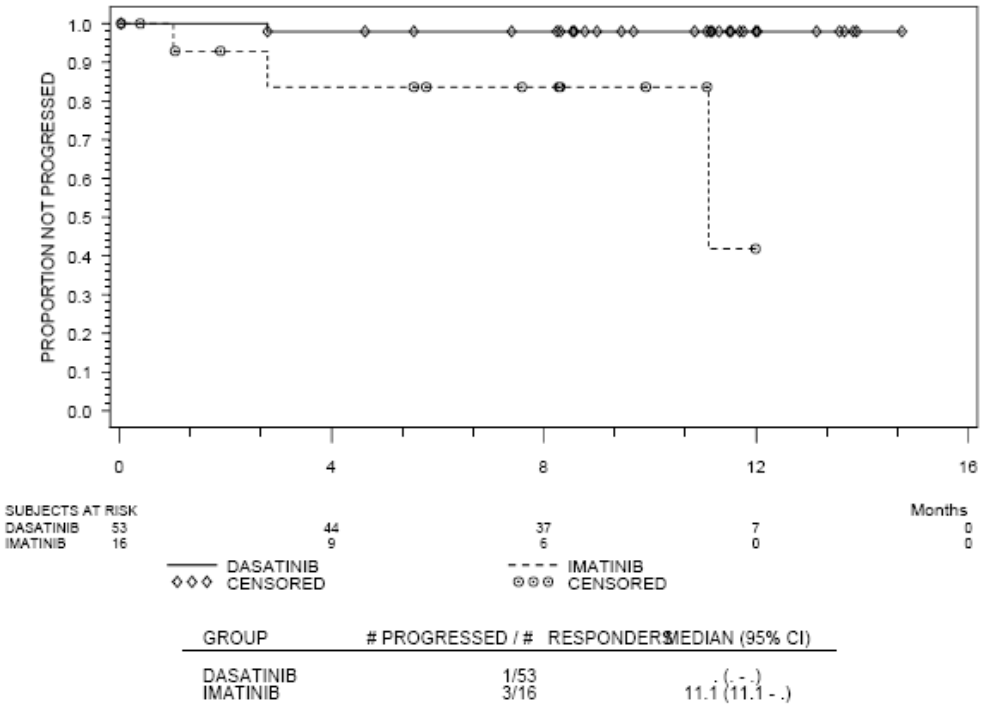
	Dasatinib (N=101) N (%)	**Imatinib (N=49) N (%)**
MCyR (12wks)	36 (36%)	14 (29%)
CCyR (12 wks)	22 (22%)	4 (8%)
MCyR (any time prior to crossover)	53 (52%)	16 (33%)
CCyR(any time prior to crossover)	40 (40%)	8 (17%)

The effects of the protocol violations or deviations on the MCyR rates at 12 weeks were evaluated. With exclusion of those patients, as illustrated in Table 28, the MCyR rates at 12 weeks remains basically unchanged in the dasatinib arm as compared in the imatinib arm.

Table 28: The MCyR Rates with Exclusion of the Patients with Significant Protocol Violations/Deviations in CA180017		
	Dasatinib (N=101) N (%)	**Imatinib (N=49)** N (%)
MCyR (12wks)	34/91 (37%)	13/47 (28%)

The duration of MCyR was not well established based on the data submitted, although the observed ranges of their durations were similar between the two arms, 0.03~14.8 months in the dasatinib arm vs 0.03~12.0 months in the imatinib arm. One of 53 MCyR responders in the dasatinib arm and three of 16 MCyR responders in the imatinib arm progressed. The Sponsor's estimate of the MCyR duration is shown in Figure 1.

Figure 1: **The Sponsor's Estimated Duration of Major Cytogenetic Response in CA180017**



Regarding PFS, there were 6/101 (6%) patients in the dasatinib arm and 10/49 (20%) in the imatinib arm who had progressed. A preliminary

estimation of PFS between the two arms appeared to be pre-mature at the present.

Post-Cross Over Efficacy: The MCyR and CHR rates were also evaluated in those patients who crossed over to the alternative arm treatment for disease progression, lack of response, or intolerance to study drug. There were 15 patients from the dasatinib arm to the treatment with imatinib and 39 patients from the imatinib arm to the treatment with dasatinib. Their responses in MCyR and CHR are shown in Table 29. It appears that dasatinib was more active in eliciting a response as compared to imatinib in this population of patients.

Table 29: Responses in Patients who Crossed Over Treatment in CA180017

	Imatinib to Dasatinib (N=39)	**Dasatinib to Imatinib (N=15)**
MCyR (post-crossover) CCyR	17 (44%) 11 (29%)	2 (15%) 0 (0 %)
CHR	36 (92%)	8 (53%)

D. Efficacy Conclusions

The efficacy review of both data and analyses for the current sNDA was primarily based on study CA180034, a two-by-two randomized open label Phase 3 study designed to optimize dasatinib dose schedule in treatment of patients with imatinib-resistant CP CML . The results demonstrated that dasatinib administered at QD schedule exhibited comparable MCyR rates compared to dasatinib administered at BID schedule and that a total daily dose of 100 mg was also similar to a total daily dose of 140 mg in attaining a MCyR. However, there were 4~10% more patients in the 100 mg TDD arms, as compared to those in the 140 mg TDD arms, who required dose escalation for lack of responses. The duration of MCyR by schedule and dose remained unknown because of few events of progression. Overall, the efficacy results of CA180034 are supportive of the new dasatinib dose schedule, 100 mg QD, for patients with CP CML whose disease is imatinib-resistant or who are not tolerant to imatinib.

The other study CA180017 was a randomized phase 2 study comparing the 12-week MCyR rates of dasatinib (70 mg BID) vs imatinib (400 mg BID) in patients with CP Ph+ CML whose disease was resistant to the regular doses (400-600 mg/day) of imatinib. Its results showed that

dasatinib at 70 mg BID appeared to be effective in this population of patients, and might be more active than the high dose of imatinib in inducing a MCyR. The reported follow-up of MCyR duration was short due to the database lock in an ongoing study, thus there remains a need for further follow-up. Overall, these results provided the preliminary evidence for efficacy comparison between dasatinib and the higher dose of imatinib in patients with CP CML resistant to the regular doses of imatinib.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The safety review of this sNDA is based on the two submitted studies CA180034 and CA180017 and the pooled safety population of 2182 dasatinib-treated patients from 8 clinical trials.

CA180034 was intended to compare the safety profiles among the four different dasatinib dose schedules (100 mg QD, 140 mg QD, 50 mg BID, and 70 mg BID) in patients with CP CML. The safety analyses show that the 100 mg QD, as compared to the other three dose schedules, was associated with lower incidences of pleural effusion, anemia, neutropenia, and thrombocytopenia and that most of other treatment associated adverse reactions were generally comparable among the four dose schedules. Compared to the current recommended dose schedule 70 mg BID, the 100 mg QD dosing had at least 8% less occurrences of all Grade pleural effusion and Grade 3/ 4 thromobocytopenia and neutropenia. In addition, there were lower rates of dose modification and discontinuation due to adverse reactions in the 100 mg QD cohort relative to the other three dose schedule cohorts. Overall, dosing dasatinib at 100 mg QD was associated with improved tolerability and safety of dasatinib in patients with imatinib-resistant CP CML or imatinib intolerance.

Study CA180017 compared the safety of dasatinib at 70 mg BID vs imatinib at 400 mg BID in patients with CP CML resistant to prior imatinib at 400-600 mg/day. Prior to crossover, dasatinib, as compared to imatinib, was basically associated with more incidences of most of hematologic and non-hematologic ARs. This might be partly related to the patient selection and the longer time of exposure to dasatinib. In general, imatinib at dose 400 mg BID was tolerated better than dasatinib 70 mg BID in patients with imatinib-resistant CP CML.

The overall safety profile of dasatinib was re-evaluated with the pooled population of 2182 dasatinib-treated patients in clinical trials. The important dasatinib-associated adverse reactions continue to be pleural effusion, hemorrhage, gastrointestinal intolerance, and myelosuppression.

B. Description of Patient Exposure

The tabulations of patient exposure and the safety analyses as described below are based on the data of 120-day safety update, which would bring up more comprehensive safety information.

Study CA180034

There were 662 patients in total who were treated in the study among 670 randomized patients. Those without any treatment are excluded for the safety analysis. The distribution of treated patients in the four dose schedule arms and their extents of dasatinib exposure are listed in Table 30. Different from the initial sNDA submission, one patient (CA180034-138-34373, with minimal cytogenetic resposne) in the 100 mg QD arm was switched from the 50 mg BID arm in the safety update, since this pa tient actually took dasatinib 50 mg BID in error.

Table 30: Extent of Dasatinib Exposure in the Safety Population of CA180034

	100 mg QD (N=165)	140 mg QD (N=163)	50 mg BID (N=167)	70 mg BID (N=167)
Duration Median (ms) (range)	11.7 (1.0-17.9)	11.3 (0.2-19.3)	11.6 (0.2-19.3)	11.5 (0.1-19.5)
Average daily dose (mg)	98.8	122.6	95.6	119.2

Patients with dose modification, interruption, and discontinuation during the trial are charted in Table 31. The major reasons for dose interruption, discontinuation, or reduction were due to adverse reactions. In contrast, the dose escalation was for lack of response, including no decrease in white cells after one month, no CHR after 3 month, no MCyR after 6 months, or no CCyR after 12 months.

Table 31: Dosing Modifications in CA180034

	100 mg QD (N=165)	140 mg QD (N=163)	50 mg BID (N=167)	70 mg BID (N=167)
Dose Interruption	95 (58%)	113 (69%)	111 (66%)	119 (71%)
Dose Discontinuation	9 (5%)	19 (12%)	18 (11%)	22 (13%)
Dose Reduction	55 (33%)	88 (54%)	75 (45%)	96 (58%)
Dose Escalation	30 (18%)	19 (12%)	26 (16%)	14 (8%)

Reviewer's Comments:
The medical reviewer calculated and verified the information of exposure and dose modifications as listed above. The durations of exposure appear balanced among the fours arms, whereas the best average dasatinib dosing near randomized doses is in the 100 mg QD arm. On the other hand, dose interruption, discontinuation, and reduction are noticeably lower in the 100 mg QD arm as compared to other three arms, suggesting that the 100 mg once daily was relatively more tolerable in the study. Overall, the information as shown in Table 31 suggests that the 100 mg QD dose schedule has a better dosing deliverability.

Study CA180017
All of the 150 patients randomized in this study were treated. Prior to crossover, 101 patients were treated with dasatinib 70 mg BID, 49 with imatinib 400 mg BID. Their extents of exposure are shown in Table 32. Dosing modification information are summarized in Table 33. Dasatinib dose escalation (to 90 mg BID) was for lack of response as listed in the prior section; however, imatinib was not allowed in the protocol to escalate for lack of response.

Table 32: Extent of Exposure in CA180017

	Dasatinib (N=101)	Imatinib (N=49)
Median Duration (ms) (Range)	13.7 (0.2-19.3)	3.1 (0.2-15.6)
Average Daily Dose (mg)	103	796

Table 33: Dosing Modifications in CA180017

	Dasatinib (N=101)	Imatinib (N=49)
Dose Interruption	84 (83%)	16 (33%)
Dose Discontinuation*	13 (13%)	9 (18%)
Dose Reduction	67 (66%)	6 (12%)
Dose Escalation	33 (33%)	0

* due to adverse reactions for dasatinib; the majority of discontinuations in the imatinib arm were due to disease progression or no MCyR.

Reviewer's Comments:

Patients in the imatinib arm had much shorter exposure to imatinib with lower rates of dose interruption and reduction, as compared to those in the dasatinib arm. This is most likely related to the cross-over due to disease progression. On the other side, the average dasatinib daily dose was close to 100 mg due to frequent dose interruption and dose reduction. This is consistent with the dosing tendency of dasatinib observed in the patients who had a total daily dose of 140 mg in study CA180034, suggesting that a total daily dose of dasatinib below 140 mg or around 100 mg is a tolerable dose.

C. Methods and Specific Findings of Safety Review

Adverse reactions recorded in MedDRA preferred terms are analyzed based on the 120-day updated datasets of these two studies, which were submitted in September 2007. In addition, the updated datasets for the overall dasatinib-treated population of 2182 patients were also analyzed for labeling revision of adverse reactions, which is discussed in the next section of this chapter. A treatment-emergent adverse reaction (TEAR) was defined as any new adverse reaction after the first dose of dasatinib and before 30 days after the last dose; whereas a drug-related adverse reaction (DRAR) was defined as any AR with causal relationship to the drug, classified by investigators as "certain", "probable", and "possible" in the datasets. Adverse reactions designated as "not likely" or "not related" in causality were not considered to be drug-related.

Study CA180034

Of the 662 patients treated, 633 patients had at least one TEAR regardless of causality. The clinically significant TEARs or DRARs in at least 10% of patients are listed in Tables 34 and 35, respectively. The important laboratory abnormalities regardless of causality are shown in Table 36.

Table 34: Clinically Significant Treatment-Emergent Adverse Reactions in CA180034 Regardless of causality (% of patient) (expanded based on the sponsor's analysis)

	100 mg QD		140 mg QD		50 mg BID		70 mg BID	
	n=165		n=163		n=166		n=167	
	All Grades	**Grade ¾**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Headache	41%	<1%	39%	3%	32%	<1%	42%	3%
Diarrhea	32%	2%	38%	3%	37%	4%	41%	6%
Fatigue	30%	2%	29%	2%	29%	0	21%	3%
Fluid Retention	27%	4%	39%	6%	29%	4%	37%	7%
Superficial localized edema	16%	0	19%	1%	19%	0	22%	0
Pleural effusion	10%	2%	21%	3%	16%	3%	20%	3%
Generalized edema	1%	0	4%	0	1%	0	6%	3%
Congestive heart failure/cardiac dysfunction[a]	1%	1%	4%	2%	1%	1%	6%	3%
Pericardial effusion	1%	<1%	4%	1%	2%	1%	2%	1%
Pulmonary edema	1%	0	0	0	1%	0	2%	1%
Pulmonary hypertension	0%	0	0	0	0	0	2%	1%
Cough	25%	0	21%	<1%	22%	0	25%	0
Nausea	22%	<1%	26%	2%	28%	<1%	35%	2%
Arthralgia	22%	2%	21%	0	19%	<1%	13%	3%
Rash	22%	2%	31%	<1%	25%	1%	26%	2%
Dyspnea	19%	2%	23%	7%	25%	6%	22%	4%
Pyrexia	15%	3%	25%	0	22%	1%	21%	<1%
Myalgia	15%	0	15%	<1%	10%	0	11%	<1%
Hemorrhage	14%	2%	21%	2%	14%	2%	19%	2%
Gastrointestinal bleeding	4%	1%	5%	1%	5%	2%	5%	2%
Vomitting	13%	<1%	18%	2%	14%	2%	26%	1%
Arrhythmia[b]	11%	0	10%	1%	7%	<1%	19%	2%

a Includes ventricular dysfunction, cardiac failure, cardiac failure acute, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and left ventricular failure.

b includes arrhythmia, arrhythmia supraventricular, atrial fibrillation, atrial flutter, bundle Branco block, palpitation, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, tachycardia, ventricular arrhythmia, and ventricular extrasystoles.

Table 35: Clinically Important Drug-Related Adverse Reactions in CA180034 (% of patient) (expanded based on the sponsor's analysis)

	100 mg QD		140 mg QD		50 mg BID		70 mg BID	
	n=165		n=163		n=166		n=167	
Adverse Reaction*	**All Grades**	**Grade ¾**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Headache	32%	<1%	28%	1%	20%	0	28%	2%
Fluid Retention	24%	2%	33%	4%	27%	4%	32%	5%
Superficial localized edema	14%	0	14%	1%	14%	0	16%	0
Pleural effusion	10%	2%	20%	2%	16%	3%	18%	2%
Generalized edema	1%	0	3%	0	0%	0	1%	0
Congestive heart failure/cardiac dysfunction[a]	0	0	2%	1%	1%	1%	4%	2%
Pericardial effusion	1%	<1%	4%	1%	2%	1%	2%	1%
Pulmonary edema	0	0	0	0	1%	0	1%	1%
Pulmonary hypertension	0%	0	0	0	0	0	1%	1%
Diarrhea	23%	1%	26%	2%	26%	3%	25%	4%
Fatigue	21%	2%	21%	2%	16%	0	17%	3%
Nausea	18%	<1%	20%	<1%	19%	<1%	27%	<1%
Rash	15%	1%	23%	<1%	19%	1%	19%	2%
Dyspnea	13%	2%	18%	6%	21%	5%	14%	4%
Myalgia	13%	0	12%	0	3%	0	7%	<1%
Arthralgia	11%	<1%	9%	0	8%	0	8%	2%
Hemorrhage	10%	1%	12%	1%	9%	2%	14%	2%
Gastrointestinal bleeding	1%	1%	2%	0	4%	2%	4%	2%
Vomitting	7%	<1%	9%	<1%	8%	0	11%	0
Pyrexia	5%	<1%	13%	0	8%	<1%	10%	<1%

* Includes those designated as certain, probable, and possible in causality.

a Includes ventricular dysfunction, cardiac failure, cardiac failure acute, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and left ventricular failure.

Table 36: Grades 3/4 Laboratory Abnormalities in CA180034

	100 mg QD (N=165)	**140 mg QD (N=163)**	**50 mg BID (N=167)**	**70 mg BID (N=167)**
Hematology Parameters				
Neutropenia	34%	43%	46%	43%
Thrombocytopenia	22%	40%	34%	38%
Anemia	10%	19%	18%	17%
Biochemistry Parameters				

Table 36: Grades 3/4 Laboratory Abnormalities in CA180034

	100 mg QD (N=165)	140 mg QD (N=163)	50 mg BID (N=167)	70 mg BID (N=167)
Hypophosphatemia	8%	6%	7%	7%
Hypocalcemia	2%	3%	1%	2%
Elevated SGPT (ALT)	0	1%	1%	1%
Elevated SGOT (AST)	1%	1%	0	0
Elevated Bilirubin	1%	2%	0	1%
Elevated Creatinine	0	1%	0	1%

With respective to cardiac adverse reactions, incidences of Grade 3 or 4 abnormalities are reviewed and the number of patients with each abnormality is shown in Table 37. Of those patients, incidences of drug-related Grade 3 or 4 abnormalities are shown in Table 38.

Table 37: Incidences of Grades 3/4 Cardiac Adverse Reactions in CA180034 (Regardless of Relationship to Drug)

	100 mg QD (N=165)	140 mg QD (N=163)	50 mg BID (N=167)	70 mg BID (N=167)
Cardiac Arrest	0	1	0	0
Arrhythmia	0	2	1	2
Ischemic Cardiac Disorders	1	3	2	1
Congestive heart failure/Cardiac dysfunction	1	3	1	7
Total	**2 (1.2%)**	**9 (5.5%)**	**4 (2.4%)**	**10 (6.1%)**

Table 38: Incidences of Drug-Related Grades 3/4 Cardiac Adverse Reactions in CA180034

	100 mg QD (N=165)	140 mg QD (N=163)	50 mg BID (N=167)	70 mg BID (N=167)
Cardiac Arrest	0	0	0	0
Arrhythmia	0	1	0	1
Ischemic Cardiac Disorders	1	2	1	0
Congestive heart failure/Cardiac dysfunction	0	1	1	4
Total	**1 (0.6%)**	**4 (2.4%)**	**2 (1.2%)**	**5 (3.0%)**

Reviewer's Comments

With examining the updated datasets of CA180034, the medical reviewer concurs with most of those analyses as presented in Tables 34, 35, and 36. The differences were double checked and corrected, such as in the incidence of rash. The reviewer also analyzed and tabulated arrhythmia as well as other significant cardiac reactions in the study, as shown in Tables 37 and 38. Overall, the safety findings of this study are basically consistent between the TEARs and DRARs; however, the incidence rates of DRARs are clearly lower as compared to that of TEARs.

With the objective of this study, the reviewer has focused on examining differences and comparability in the dasatinib safety profile associated with each of the four different dose schedules. As shown in Table 35, most of non-hematologic ARs were generally comparable among the four arms. As a key dasatinib-associated adverse reaction, pleural effusion of all grade in the 100 mg QD arm occurred 6% lower than in the 50 mg BID arm, 8% lower than in the 70 mg BID, and 10% lower than in 140 mg QD arms; however, incidences of Grade 3/ 4 pleural effusion appeared to be similar across the arms, suggesting that the observed lower incidence of all grades of pleural effusion in the 100 mg QD arm is most likely from a decrease in the incidence of Grade 1 or 2 pleural effusion. The rates of overall fluid retention in the 100 mg daily dose arms are also considerably lower than that in the 140 mg daily dose arms. Although few Grade 3/ 4 cardiac events occurred, as shown in Tables 37 and 38, cardiac dysfunction and congestive heart failure occurred less frequently with the 100 mg daily doses as compared to the 140 mg daily doses. Since the median safety follow-up for the study was short, only about one year, continued follow-up on safety is necessary for making a final conclusion.

Unlike the differences in non-hematologic ARs, the clinically important hematologic ARs showed evident differences, favoring the 100 mg dose schedule. As shown in Table 36, both Grade 3/ 4 neutropenia and thrombocytopenia occurred 10-15 % lower in the 100 mg QD arm compared to the other arms. These differences also suggest that the dasatinib-related bone marrow suppression relates to both a schedule and a dose of dasatinib.

Taken together, the evidence demonstrates that dosing dasatinib at 100 mg QD was associated with reduced incidences of the key side effects of dasatinib such as neutropenia, thromobocytopenia, and pleural effusion.

Study CA180017

The safety information prior to crossover was analyzed in all 150 patients who were treated as randomized. One patient in the dasatinib arm and four in the imatinib arm did not have any adverse reaction reported while on study. The adverse reactions mostly relevant to the two drugs are listed in Tables 39 and 40. The frequent important laboratory abnormalities are summarized in Table 41.

Table 39: Selected Treatment-emergent Adverse Events in CA180017

	Dasatinib 70 mg BID (N=101)		Imatinib 400 mg BID (N=49)	
	All Grades	**Grade 3/4**	**All Grades**	**Grade 3/4**
Diarrhea	48%	2%	29%	2%
Fluid Retention	39%	8%	47%	0
Pleural Effusion	24%	5%	0	0
Superficial Localized Edema	22%	1%	45%	0
Generalized Edema	4%	0	4%	0
Congestive Heart Failure/Cardiac Dysfunction	3%	2%	0	0
Pericardial Effusion	1%	0	0	0
Pulmonary Edema	2%	2%	0	0
Pulmonary Hypertension	1%	0	0	0
Nausea	31%	0	39%	0
Hemorrhage	27%	2%	16%	0
Gastrointestinal Bleeding	5%	2%	2%	0
Vomiting	16%	0	0	0

Table 40: Selected Drug-Related Adverse Events in CA180017

	Dasatinib 70 mg BID (N=101)		Imatinib 400 mg BID (N=49)	
	All Grades	**Grade 3/4**	**All Grades**	**Grade 3/4**
Diarrhea	37%	2%	29%	2%
Fluid Retention	36%	7%	43%	0
Pleural effusion	23%	5%	0	0
Superficial localized edema	17%	1%	41%	0
Generalized edema	2%	0	4%	0
Congestive heart failure/cardiac dysfunction	2%	1%	0	0
Pericardial effusion	1%	0	0	0
Pulmonary edema	3%	2%	0	0
Pulmonary hypertension	1%	0	0	0
Nausea	24%	0	33%	0
Hemorrhage	18%	1%	8%	0
Gastrointestinal Bleeding	3%	1%	0	0
Vomiting	10%	0	24%	0

Table 41: Grades 3/4 Laboratory Abnormalities in CA180017		
	Dasatinib 70 mg BID (N=101)	**Imatinib 400 mg BID (N=49)**
Neutropenia	63%	39%
Thrombocytopenia	56%	14%
Anemia	18%	8%
Hypophosphatemia	19%	24%
Hypocalcemia	4%	0%
Elevated SGPT (ALT)	2%	0
Elevated SGOT (AST)	1%	0
Elevated Bilirubin	1%	0
Elevated Creatinine	0	0

Reviewer's Comments

Study CA180017 was to compare efficacy and safety of dasatinib at the current recommended dose schedule 70 mg BID with that of imatinib at 400 mg BID in patients with CP CML resistant to prior imatinib at 400-600 mg/day. Due to this eligibility requirement and the nature of the two drugs at their planned dose schedules, it is not surprised to see higher incidences of most of both hematologic and non-hematologic ARs with dasatinib compared with imatinib treatment prior to crossover, as shown in Tables 39, 40, and 41. The shorter time of exposure to imatinib 800 mg/day in patients treated previously with imatinib also contributed to the lower incidences of imatinib-associated ARs, which is discussed in Section of Patient Exposure.

Death

There were a total of 32 deaths (5% of the treated patients) as of the 120-day update in study CA180034. Their distribution as per the cause of death is listed in Table 42. Of the 32 patients, 12 patients died on study or within the 30 days of treatment termination, which is listed in Table 43. The on-study deaths thought by the investigators as the results of dasatinib toxicity occurred in the 70 mg BID arm, one with colon necrosis and the other with pulmonary edema, congestive heart failure, and pleural effusion.

Table 42: All Deaths in the 120-day Updated Data of CA180034

Cause of Death	100 mg QD (N=165)	140 mg QD (N=163)	50 mg BID (N=167)	70 mg BID (N=167)
Total	8	5	7	12
Drug Toxicity	0	0	0	2
Disease Progression	3	3	2	0
Cardiovascular Disease	0	1	2	1
Other (eg. bleeding, infection, suicide, or unknown)	5	1	3	9

Table 43: Deaths within 30 days of Treatment Termination in CA180034

Cause of Death	100 mg QD (N=165)	140 mg QD (N=163)	50 mg BID (N=167)	70 mg BID (N=167)
Total	2	1	5	4
Drug Toxicity	0	0	0	2
Disease Progression	0	0	1	0
Cardiovascular Disease	0	1	2	0
Other (eg. bleeding, infection, suicide, or unknown)	2	0	2	2

In study CA180017, two patients in the dasatinib arm deceased. One death within 30 days of treatment discontinuation was ascribed to multiple organ failure; the other death beyond the 30 days was due to disease progression. The was no death reported with the imatinib arm in the 120-day safety update.

Reviewer's Comments
The current data and analyses do not show the evidence suggestive of a trend or an increase of dasatinib toxicity-related death or sudden death.

D. Adequacy of Safety Testing

Dasatinib has been used in a total of 2182 patients from 8 clinical trials, including study CA180034. The sponsor also submitted the safety datasets with this sNDA for overall evaluation of dasatinib safety profile in the pooled population of 2182 patients. Beside the QD dosing in CA180034, most of the pooled patients received dasatinib 140 mg daily or less given at an equally divided dose twice daily. With a median treatment

duration of 11 months (range 0.03-26.0 months) (70% had ≥ 6 months of exposure), the updated safety analyses in the overall population are verified and summarized in Tables 44, 45, and 46. Most of the frequently observed TEARs as shown in Table 44 are similar to the observed DRARs as listed in Table 45. The DRARs with an incidence frequency of ≥20% included fluid retention, diarrhea, headache, skin rash, nausea, hemorrhage, fatigue, and dyspnea. This information would serve as a general control for estimating the sufficiency of an individual trial with dasatinib at similarly dose schedules.

Most of adverse reactions observed in study CA180034 are basically consistent with the general safety profile, especially for Grade 3/ 4 toxicities in patients with CP CML, suggesting that the current safety analysis results for CA180034 would be reliable.

Table 44: Treatment-Emergent Adverse Reactions Reported in ≥10% of All Dasatinib-Treated Patients in Clinical Studies

Adverse Reaction	All Patients (N=2182)		Chronic Phase (N=1150)	Accelerated Phase (N=502)	Myeloid Blast Phase (N=280)	Lymphoid Blast Phase and Ph+ ALL (N=250)
	All Grades	Grades 3/4	Grades 3/4	Grades 3/4	Grades 3/4	Grades 3/4
	Percent (%) of Patients					
Diarrhea	47	5	4	8	6	6
Fluid Retention	45	9	7	10	16	9
Superficial localized edema	28	1	<1	1	3	1
Pleural effusion	25	6	4	6	10	8
Other fluid retention	14	4	4	4	8	3
Generalized edema	4	1	<1	1	1	1
Congestive heart failure/cardiac dysfunction[a]	4	2	2	1	3	1
Pericardial effusion	4	1	1	1	3	0
Pulmonary edema	3	1	1	1	1	1
Ascites	1	<1	0	<1	1	1
Pulmonary hypertension	1	<1	<1	<1	1	1
Headache	39	3	2	2	4	6
Musculoskeletal Pain	38	5	3	4	7	12
Infection (including bacterial, viral, fungal, non-specified)	38	8	4	9	18	14
Hemorrhage	36	8	3	13	18	16
Gastrointestinal bleeding	15	6	2	10	12	9

Table 44: Treatment-Emergent Adverse Reactions Reported in ≥10% of All Dasatinib-Treated Patients in Clinical Studies

Adverse Reaction	All Patients (N=2182)		Chronic Phase (N=1150)	Accelerated Phase (N=502)	Myeloid Blast Phase (N=280)	Lymphoid Blast Phase and Ph+ ALL (N=250)
	All Grades	Grades 3/4	Grades 3/4	Grades 3/4	Grades 3/4	Grades 3/4
	Percent (%) of Patients					
CNS bleeding	2	1	0	<1	1	3
Pyrexia	36	3	1	4	8	6
Fatigue	34	4	2	5	4	7
Skin Rash[b]	33	1	1	1	1	2
Nausea	32	1	1	1	3	3
Dyspnea	31	7	6	7	9	7
Upper Respiratory Tract Infection/Inflammation	30	1	1	1	3	1
Cough	29	<1	<1	<1	<1	0
Pain	24	2	1	1	4	2
Vomiting	24	2	1	2	1	3
Abdominal Pain	22	3	2	2	6	4
Arthralgia	21	2	2	1	3	2
Anorexia	16	1	<1	1	2	1
Mucosal Inflammation (including mucositis/stomatitis)	15	1	<1	<1	2	1
Asthenia	14	2	<1	3	4	3
Weight Decreased	14	1	1	1	2	<1
Constipation	13	<1	<1	<1	<1	1
Dizziness	13	<1	<1	<1	0	<1
Myalgia	13	1	<1	1	1	1
Chest Pain	12	1	1	<1	3	2
Pneumonia (including bacterial, viral, and fungal)	12	7	4	9	12	8
Pruritus	11	<1	0	<1	0	0
Weight Increase	11	1	<1	1	1	1
Arrhythmia[C]	10	1	1	1	2	2

[a] Includes ventricular dysfunction, cardiac failure, cardiac failure acute, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and left ventricular failure.

[b] Includes erythema, erythema multiforme, erythrosis, exanthem, exfoliative rash, generalized erythema, genital rash, heat rash, milia, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, skin exfoliation, skin irritation, systemic lupus erythematosus rash, toxic skin eruption, urticaria vesiculosa, drug eruption, and rash vesicular.

[C] includes arrhythmia, arrhythmia supraventricular, atrial fibrillation, atrial flutter, bundle Branco block, palpitation, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, tachycardia, ventricular arrhythmia, and ventricular extrasystoles.

Table 45: Drug-Related Adverse Events Reported in ≥10% of All Dasatinib-Treated Patients in Clinical Studies

Adverse Reaction	All Patients (N=2182)		Chronic Phase (N=1150)	Accelerated Phase (N=502)	Myeloid Blast Phase (N=280)	Lymphoid Blast Phase and Ph+ ALL (N=250)
	All Grades	Grades 3/4	Grades 3/4	Grades 3/4	Grades 3/4	All Grades
	Percent (%) of Patients					
Fluid Retention	37	8	6	7	13	7
Superficial localized edema	20	<1	<1	1	1	<1
Pleural effusion	22	5	4	5	10	6
Other fluid retention	10	3	3	3	6	2
Generalized edema	3	<1	<1	1	<1	1
Congestive heart failure/cardiac dysfunction	2	1	2	<1	2	1
Pericardial effusion	3	1	1	1	2	0
Pulmonary edema	2	1	1	1	1	1
Ascites	<1	<1	0	0	1	<1
Pulmonary hypertension	1	<1	<1	0	1	1
Diarrhea	31	3	3	4	5	4
Headache	24	1	1	1	1	2
Skin Rash	22	1	1	1	1	1
Nausea	22	1	1	1	2	2
Hemorrhage	21	6	2	11	12	8
Gastrointestinal bleeding	7	4	1	8	9	5
CNS bleeding	1	<1	0	<1	<1	2
Fatigue	21	2	2	3	1	2
Dyspnea	20	4	5	4	5	2
Musculoskeletal Pain	14	1	2	1	1	<1
Pyrexia	13	1	1	2	3	1
Vomiting	13	1	1	1	1	2
Abdominal Pain	10	1	1	<1	1	2

Table 46: Important Grades 3/4 Laboratory Abnormalities in Clinical Studies

	Chronic Phase (N=1150)	Accelerated Phase (N=502)	Myeloid Blast Phase (N=280)	Lymphoid Blast Phase and Ph+ ALL (N=250)
	Percent (%) of Patients			
Hematology Parameters				
Neutropenia	46	68	80	78
Thrombocytopenia	41	71	81	78
Anemia	18	55	75	45
Biochemistry Parameters				
Hypophosphatemia	11	15	19	22
Hypocalcemia	2	8	16	11
Elevated SGPT (ALT)	1	3	6	7
Elevated SGOT (AST)	1	1	4	5
Elevated Bilirubin	<1	1	4	5
Elevated Creatinine	<1	2	3	1

The important safety limitations of study CA180034 are related to the exclusion criteria of the study, which excluded patients with significant cardiac or bleeding histories. Therefore, the safety and tolerability of dasatinib in patients with those disorders remains unknown. Since the median duration of treatment in the study was only about a year, continued monitoring of safety with long-term use of dasatinib would be important, given many of patients with CML are elderly with cardiac risk factors or cormobidities. Furthermore, there was no information about the safety in patients with hepatic or renal impairment because of the eligibility criteria of the study.

E. Summary of Critical Safety Findings and Limitations of Data

The safety review of this sNDA is based on three groups of dataset for study CA180034, study CA180017, and the pooled safety population of 2182 dasatinib-treated patients from 8 clinical trials.

CA180034 is the key study for this sNDA and provides the evidence for a new dose and schedule of dasatinib for treatment of patients with CP CML. The main safety concern of the study was about any differences in adverse reaction among the four different dose schedules, 100 mg QD, 140 mg QD, 50 mg BID, and 70 mg BID. The safety analyses show that the 100 mg QD was associated with lower incidences of pleural effusion, neutropenia, thrombocytopenia, and anemia, as compared to the other three dose schedules, and that most of other treatment associated

adverse reactions were generally comparable among the four dose schedules. Compared to the current recommended dose schedule 70 mg BID, the 100 mg QD dosing had at least 8% less occurrences of all Grade pleural effusion and Grade 3/ 4 thromobocytopenia and neutropenia. These reduced incidences in the key dasatinib side effects appeared to be correlated with the observed lower rates of dose interruption, reduction, or discontinuation due to adverse reactions in the 100 mg QD cohort relative to the other three dose schedule cohorts. In general, dosing dasatinib at 100 mg QD was associated with improved tolerability and reduced incidences in the key adverse reactions of dasatinib in patients with CP CML.

Study CA180017 provides the data for comparing the safety of dasatinib at 70 mg BID vs imatinib at 400 mg BID in patients with CP CML resistant to prior imatinib at 400-600 mg/day. The safety analyses on the data prior to crossover show that dasatinib, as compared to imatinib, was associated with higher incidences of most of hematologic and non-hematologic ARs. The shorter time of exposure to imatinib due to disease progression and prior tolerance to conventional doses of imatinib likely contributed the safety differences in addition to the nature of the drugs.

The overall safety profile was updated with the pooled population of 2182 dasatinib-treated patients in clinical trials. The important clinical dasatinib-associated ARs remains to be pleural effusion, hemorrhage, gastrointestinal intolerance, and myelosuppression.

In general, the safety data of dasatinib did not provide information on patients with significant cardiac history or bleeding, hepatic or renal impairment as they were ineligible for the dasatinib trials. In addition, the median times of exposure to dasatinib in CA180034 or the pooled population of 2182 dasatinib-treated patients are still relatively short (only about 11-12 months), long-term safety information remains to be collected. Continued monitoring of dasatinib safety in those trials is very important.

VIII. Dosing, Regimen, and Administration Issues

Dasatinib is administered orally at a dose of 100 mg once daily. Tablets should not crushed or cut, and should be swallowed whole.

There is no specific pre-medication required for the treatment.

IX. Use in Special Populations

A. Evaluation of Gender Effects and Adequacy of Investigation

There was no gender effects found in the initial approval of dasatinib.

A gender-based analysis was performed at the FDA on study CA180034, since it was not discussed in the submission. The distribution of male and female patients in each dose schedule studied was basically comparable in percentage. The differences in gender-based MCyR rate appeared to be within 5%, regardless of dose schedules. Therefore, dose schedules may not have a significant relation with genders. The analysis is preliminary.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Of the 670 patients randomized in CA180034, 179 (27%) were 65 years of age or older. Regardless of doses and schedules, the overall MCyR rate in this population of patients was 45%, compared to a MCyR rate of 60% in the patients <65 years old. The difference is 15% (95% CI: 6.7%~23.7%). Similar differences between the two age groups in MCyR rate exist in all fours dose schedules. In the 100 mg QD schedule, the MCyR rate was 14% less in patients $\geq$65, similar to that seen in the 70 mg BID schedule.

With respective to Race, no analysis on efficacy and safety has been done for the small sample sizes of the minorities in this trial.

C. Evaluation of Pediatric Program

The safety and effectiveness of dasatinib have not been established in the pediatric population. No information in this sNDA was about this population.

D. Comments on Data Available or Needed in Other Populations

Dasatinib has not been evaluated in patients with hepatic or renal impairment.

Clinical Review Section

X. Conclusions and Recommendations

A. Conclusions

This supplemental new drug application (sNDA 021986) is mainly for a new dose and schedule of dasatinib, which is based on the results of study 180034, an open-label, randomized Phase 3 study with a two-by-two factorial design to evaluate the differences in dasatinib efficacy/safety between two schedules (QD and BID) or two doses (100 mg and 140 mg) in patients with imatinib-resistant CP CML or patients with imatinib intolerance. A total of 670 patients were randomized approximately equally to each of the four dose schedules in this study. The median treatment time for each dose schedule was 11 months, with a minimum follow-up of 6 months. Efficacy evaluations are based on the data of the sNDA submission, whereas safety analyses are based on the data of the 120-day safety update.

Efficacy

The primary efficacy endpoint of CA180034 was to compare the rate of 6-month MCyR by schedule and dose. The results demonstrated that dasatinib administered at the QD schedules exhibited comparable MCyR rates compared to dasatinib administered at the BID schedules and that a total daily dose of 100 mg was similar to a total daily dose of 140 mg in attaining comparable MCyR rates. However, as compared to the patients in the 140 mg TDD arms, there were 4~10% more patients in the 100 mg TDD arms who required dose escalation for lack of treatment responses. The preliminary evidence also suggested that the duration of MCyR appeared to be similar by schedule and dose. Although few more patients in the 100 mg QD schedule required to escalate their dose to 140 mg QD for lack of treatment response, the efficacy results of this study are supportive of the newly proposed dasatinib dose schedule, 100 mg QD, in treatment of patients with CP CML whose disease is resistant to or who are intolerant to imatinib.

Safety

Based on the 120-day safety update data of CA180034, the safety analyses of the four different dasatinib dose schedules (100 mg QD, 140 mg QD, 50 mg BID, and 70 mg BID) were performed. The results showed that the 100 mg QD, as compared to the other three dose schedules, was associated with lower incidences of pleural effusion, anemia, neutropenia, and thrombocytopenia, while most of the remainder of treatment associated or drug-related adverse reactions were generally comparable among the four dose schedules. Compared to the current recommended

dose schedule 70 mg BID, the 100 mg QD dosing had at least 8% less occurrences of all Grade pleural effusion and Grade 3/ 4 thromobocytopenia and neutropenia. The decreases in these adverse reactions appeared to be associated with the lower rates of dose modifications or discontinuation due to adverse reactions in the 100 mg QD schedule relative to the other three dose schedules. Overall, dosing dasatinib at 100 mg QD was associated with improved tolerability and safety profile of dasatinib in patients with CP CML with resistance or intolerance to imatinib.

B. Recommendations

This dasatinib sNDA 021986 provided adequate evidence supporting a dose and schedule of dasatinib for the treatment of patients with chronic phase chronic myeloid leukemia resistant to or who were intolerant to imatinib. The reviewer found that both the Sponsor's data and results of the analyses were generally reliable. Since dasatinib has been approved, the new dose schedule should improve patient's tolerability and reduce the key dasatinib-associated adverse reactions, without significant decline in its efficacy. The balance of benefit/risk of the new dose schedule should be adjusted by health care providers through close monitoring both patient's response and tolerance. Since the overall follow-up time is still short, about 11~12 months, and the long-term efficacy and safety profile of the study remain to be defined, the accelerated approval of this new dose and schedule of dasatinib is therefore recommended for the treatment of patients with chronic phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib. The Sponsor must provide additional follow-up on both efficacy and safety to convert to regular approval.

XI. Appendix

None

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/s/

Yang-Min Ning
11/7/2007 12:53:34 PM
MEDICAL OFFICER

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11/7/2007 01:44:22 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-986/S001 & 002

CHEMISTRY REVIEW(S)

OFFICE OF NEW DRUG QUALITY ASSESSMENT
DIVISION OF POST-MARKETING EVALUATION
CHEMISTRY REVIEW OF EFFICACY SUPPLEMENT

NDA 21-986
SPRYCEL (dasatinib)

Efficacy supplement SE2-001
Document Date: 10-May-2007
Priority Review Action Date: 11-Nov-2007

Chemistry Reviewer: Jean Salemme, Ph.D., ONDQA/DPE
Date: 16-Aug-2007

NDA 21-986
Efficacy Supplement, SE2-001
10-May-2007

Three tablets sizes, 20 mg, 50 mg, and 70 mg, are approved in the NDA. This efficacy supplement proposes a change in dose and administration from 70 mg twice a day to 100 mg once a day. No changes are proposed in the approved chemistry, manufacturing and controls.

Fileability of the Supplement
From a CMC perspective, the supplement is fileable.

Evaluation of Chemistry Information Submitted in Supplement SE2-001
The only chemistry and manufacturing information submitted in the supplement is in Item 4, Environmental Assessment.

In this section, the sponsor requests an exclusion from the requirement for an Environment Assessment, and provides a Claim for a Categorical Exclusion from the requirement for an Environmental Assessment.

Evaluation: Acceptable. The request for exclusion from the requirement for an Environmental Assessment is justified.

Overall CMC Evaluation of (b) (4) SE2-001: ACCEPTABLE

Reviewed:
Dr. Liang Zhou, Pharmaceutical Assessment Lead, Branch VIII, Division IV, ONDQA,
for Dr. Hasmukh Patel, Branch Chief, Branch VIII, Division IV, ONDQA

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/s/

Jean Salemme
8/16/2007 02:57:11 PM
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Acting for BC, Dr. Hasmukh Patel

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-986/S001 & 002

STATISTICAL REVIEW(S)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCES
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number:	21-986 / S_001
Drug Name:	SPRYCEL ® (dasatinib)
Indication:	Chronic Myeloid Leukemia (CML)
Applicant:	Bristol-Myers Squibb Company
Date:	May 10, 2007
Review Priority:	Priority
Biometrics Division:	V (HFD 711)
Statistical Reviewer:	Kun He
Concurring Reviewers:	Rajeshwari Sridhara, Ph.D., Deputy Director Aloka Chakravarty, Ph.D., Director
Medical Division:	Oncology Drug Products (HFD 150)
Clinical Team:	Max Ning, M.D., Clinical Reviewer Ann Farrell, M.D., Deputy Director
Project Manager:	Ms. Milinda Vialpando

Keywords: non-inferiority analysis

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Statistical Review and Evaluation

1. Executive Summary

1.1 Conclusions and Recommendations

The applicant submitted the data and analyses of two trials, CA180034 and CA180017 (mainly for updating the report submitted in the initial NDA), to seek a change in the dose and administration schedule for dasatinib in the treatment of subjects with chronic phase CML. The data and analyses in this supplemental NDA #21,986 demonstrated that the efficacy of dasatinib when administered QD was similar to that administered BID in the treatment of subjects with chronic phase CML and support a change in the dose and administration schedule for dasatinib in the treatment of subjects with chronic phase CML.

1.2 Brief Overview of Clinical Studies

The applicant submitted the data and analyses of two trials, CA180034 and CA180017 (mainly for updating the report submitted in the initial NDA), to seek a change in the dose and administration schedule for dasatinib in the treatment of subjects with chronic phase CML.

CA180034 was a randomized, open-label, Phase 3 study with a 2 by 2 design comparing 2 doses (100 mg and 140 mg) and 2 schedules (QD and BID) of dasatinib in subjects with chronic phase CML. Subjects with chronic phase CML previously treated with imatinib were enrolled in this study. 724 subjects were enrolled and 670 were randomized (498 imatinib-resistant, according to the assessment on the baseline case report form, and 172 imatinib-intolerant). The primary endpoint was the rate of major cytogenetic response (MCyR) with minimum follow-up of 6 months in subjects resistant to imatinib.

CA180017 was a randomized, non-comparative study of dasatinib (70 mg BID) and high-dose imatinib (400 mg BID) in subjects with chronic phase CML who were resistant to imatinib. This study enrolled subjects after failure of standard imatinib (i.e., $\leq$ 600 mg/day). Subjects were randomized in a 2:1 ratio to receive either dasatinib 70 mg BID or imatinib 800 mg/day (400 mg BID) with continuous daily treatment. 166 subjects were enrolled and 150 were randomized: 101 were randomized to dasatinib and 49 were randomized to imatinib. The primary endpoint was the rate of major cytogenetic response (MCyR) at 12 weeks in subjects resistant to imatinib. The main purpose of study CA180017 was to update the report submitted in the initial NDA.

1.3 Statistical Issues and Findings

In Study CA180034, the primary analysis was to compare a MCyR rate between imatinib-resistant subjects in the QD schedule and the BID schedule. The MCyR rate was 51.8% (95% CI 45.4% -

58.2%) for QD and 49.0% (95% CI 42.7% - 55.4%) for BID. The difference in MCyR between the QD and BID schedules in imatinib-resistant subjects was +2.8% with 95% CI (-6.0%, +11.6%), whose lower bound is greater than or equal to -15%. Whether the fixed margin -15% used in the non-inferiority analysis was clinically meaningful should be based on the clinical judgment and risk and benefit ratio.

In Study CA180017, the MCyR rate at 12 weeks was 36% (95% CI 26.4% - 45.8%) in the dasatinib group and 29% (95% CI 16.6% - 43.3%) in the imatinib group.

The data and analyses in this supplemental NDA demonstrated that the efficacy of dasatinib when administered QD was similar to that administered BID in the treatment of subjects with chronic phase CML and support a change in the dose and administration schedule for dasatinib in the treatment of subjects with chronic phase CML.

2. Introduction

2.1 Overview

SPRYCEL®(dasatinib, BMS-354825) is a potent, broad spectrum inhibitor of 5 critical oncogenic tyrosine kinases/kinase families, each of which is linked to multiple forms of human malignancies, and was discovered and developed by the applicant. SPRYCEL at 70 mg twice daily (BID) is approved in the United States (US), European Union (EU), and several other countries for the treatment of chronic myelogenous leukemia (CML) and Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL), resistant or intolerant to imatinib.

The current supplemental NDA 21,986 / S_001 was based upon one Phase 3 study (CA180034) designed to compare the dose and schedule of dasatinib for the optimal benefit/risk ratio among subjects with chronic phase CML. Efficacy results from the randomized, non-comparative Phase 2 study (CA180017) in 150 subjects with chronic phase CML were also presented as an update to the report submitted in the initial NDA.

CA180034 was a randomized, open-label, Phase 3 study with a 2 by 2 design comparing 2 doses (100 mg and 140 mg) and 2 schedules (QD and BID) of dasatinib in subjects with chronic phase CML. Subjects with chronic phase CML previously treated with imatinib were enrolled in this study. 724 subjects were enrolled and 670 were randomized (498 imatinib-resistant, according to the assessment on the baseline case report form, and 172 imatinib-intolerant). The primary endpoint was the rate of major cytogenetic response (MCyR) with minimum follow-up of 6 months in subjects resistant to imatinib.

CA180017 was a randomized, non-comparative study of dasatinib (70 mg BID) and high-dose imatinib (400 mg BID) in subjects with chronic phase CML who were resistant to imatinib. This study enrolled subjects after failure of standard imatinib (i.e., ≤ 600 mg/day). Subjects were randomized in a 2:1 ratio to receive either dasatinib 70 mg BID or imatinib 800 mg/day (400 mg BID) with continuous daily treatment. 166 subjects were enrolled and 150 were randomized: 101 were randomized to dasatinib and 49 were randomized to imatinib. The primary endpoint was the rate of major cytogenetic response (MCyR) at 12 weeks in subjects resistant to imatinib.

2.2 Data Sources

The path to the CDER Electronic Document Room (EDR) is:

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3. Statistical Evaluation

3.1 Evaluation of Efficacy

Part of the text, tables and figures presented in this section were adapted from the applicant's Study Report.

3.1.1 Study CA180034

3.1.1.1 Objective

The primary objective of this study was to compare the MCyR rates of dasatinib after a minimum follow-up of 6 months when administered QD relative to dasatinib administered BID in the treatment of subjects with CP CML resistant to imatinib.

3.1.1.2 Study Design

This was a randomized, multi-center, open-label Phase 3 study of dasatinib with a two-by-two factorial design. The chronic phase CML subjects with a history of primary or acquired resistance or intolerance to imatinib were enrolled. Subjects were stratified by imatinib-resistance or imatinib-intolerance. A permuted block design was used for randomization with a 1:1:1:1 ratio and planned to enroll a total of 87 imatinib-resistant subjects per group. Enrollment into the study continued until a minimum of 348 imatinib-resistant subjects participated. The study actually enrolled 724 subjects, of whom 670 were randomized (496 imatinib-resistant and 174 imatinib-intolerant subjects, according to the imatinib status registered in the Interactive Voice Response System [IVRS]).

Table 3.1.1.2.1 Study Design

		Schedule	
		QD	BID
Dose	100 mg TDD	Group 1 (100 mg)	Group 2 (50 mg)
	140 mg TDD	Group 3 (140 mg)	Group 4 (70 mg)

Subjects were treated until progressive disease or intolerable toxicity as determined by the treating physician. Subjects were evaluated for the efficacy and safety of dasatinib.

The main inclusion criteria included that male or female who were at least 18 years of age. Subjects considered to have Philadelphia chromosome positive (Ph+ or BCR/ABL+) if they had CP CML, resistance to imatinib, and intolerance to imatinib.

3.1.1.3 Efficacy Measures

The primary efficacy endpoint was the rate of MCyR with a minimum of 6 months of follow-up in the treatment of subjects with CP CML resistant to imatinib. The MCyR rate was defined as the proportion of subjects with a best CyR of either CCyR or PCyR.

Cytogenetic response (CyR) was based on the number of Ph+ metaphases among cells in metaphase on a bone marrow (BM) sample. Ideally, 25 metaphases but at least 20 metaphases from a BM sample were evaluated. Evaluation of the CyR using hyper metaphase fluorescent in situ hybridization (FISH) only was not accepted. The criteria for CyR were as follows:

- Complete cytogenetic response (CCyR): 0% Ph+ cells in metaphase in BM
- Partial cytogenetic response (PCyR): >0 to 35% Ph+ cells in metaphase in BM
- Minor cytogenetic response: >35 to 65% Ph+ cells in metaphase in BM
- Minimal cytogenetic response: >65 to 95% Ph+ cells in metaphase in BM
- No cytogenetic response: >95 to 100% Ph+ cells in metaphase in BM
- Best CyR was defined as the best response obtained at any time during the study
- MCyR was defined as a best CyR of CCyR or PCyR

Secondary efficacy endpoints included the rate of CHR, time to, and duration of MCyR and CHR, PFS, and OS.

3.1.1.4 Sample Size Considerations

Assuming a 50% MCyRR in the imatinib-resistant subjects on the BID schedule, the primary efficacy analysis required 174 imatinib-resistant subjects on each schedule (BID and QD) or 87 imatinib-resistant subjects per treatment group to give at least 80% power to demonstrate non-inferiority of the QD schedule relative to the BID schedule if the lower bound of the 95% CI for the difference in 6-month MCyR rates ($MCyRR_{QD}$ minus $MCyRR_{BID}$) $\geq$ - 15%.

As of the data cutoff date, 498 imatinib-resistant subjects (according to the assessment on the baseline CRF) were randomized, giving at least 90% power to deduce non-inferiority of the QD schedule relative to the BID schedule.

3.1.1.5 Interim Analysis

No formal interim analysis was planned.

Two interim analyses of MCyR rates were previously performed, testing at a nominal significance level of 0.0001: differences between dosing schedules and between TDD were provided, together with two-sided, asymptotic 99.99% CI. The use of this stopping boundary maintained a two-sided significance level of 0.05 for the main analysis. The first of these analyses was a Data and Safety

Monitoring Board [DSMB] analysis based on the first 100 subjects randomized, with a minimum of 1 month of follow-up. A second interim analysis was conducted for administrative reasons, based on the same subject cohort used for the DSMB analysis.

3.1.1.6 Statistical Analysis Methods

The primary efficacy analysis was to estimate the difference of 6-month MCyR rates between the two schedules ($MCyRR_{QD}$ minus $MCyRR_{BID}$) in the imatinib-resistant subjects in the population of all randomized subjects. If the lower bound of the asymptotic 95% CI of the difference was ≥ -15%, non-inferiority of the QD schedule relative to the BID schedule would be claimed. If the lower bound of the asymptotic 95% CI of the difference was above zero, superiority of the QD schedule relative to the BID schedule would be claimed.

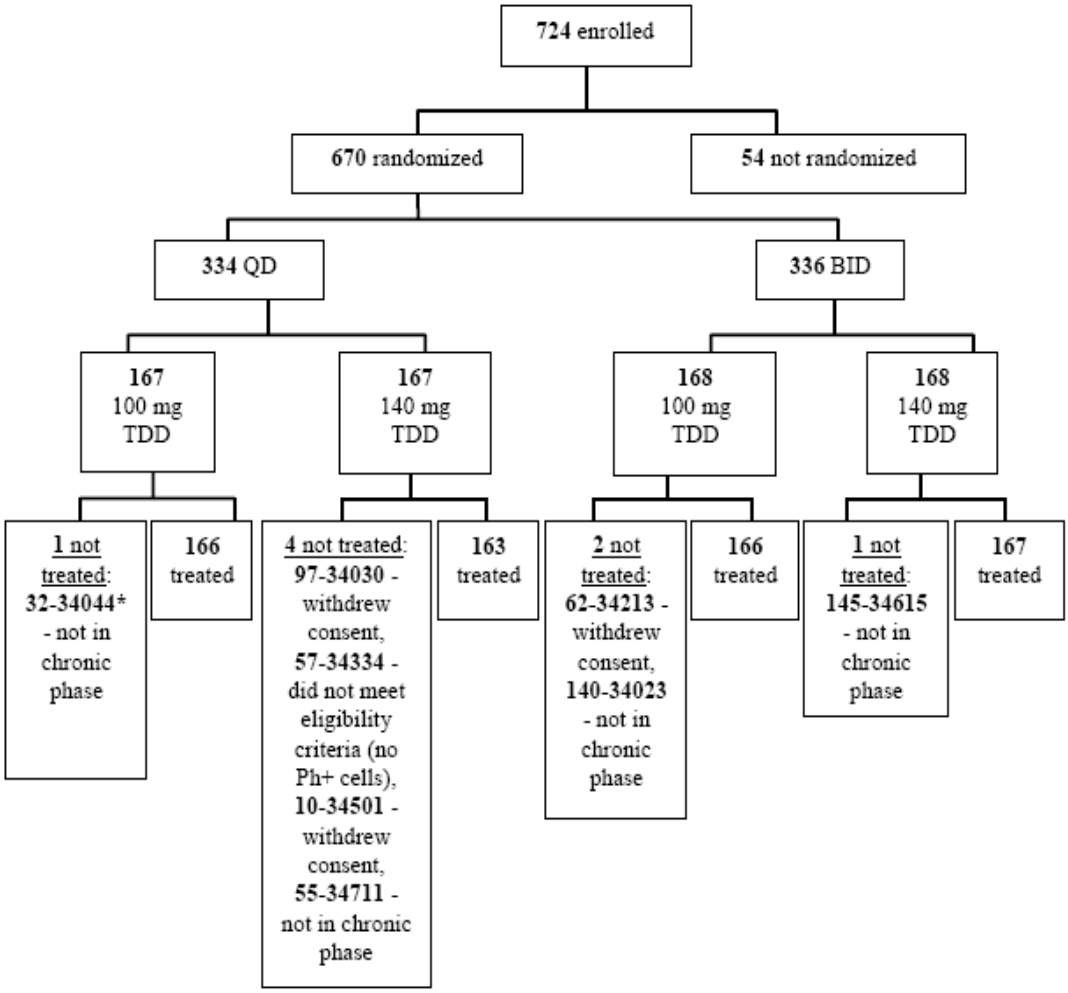
The main secondary analysis was to estimate the difference of MCyR rates between the two TDD levels ($MCyRR_{100\ mg\ TDD}$ minus $MCyRR_{140\ mg\ TDD}$) in the imatinib-resistant subjects. Asymptotic normal 95% CIs for the differences in MCyR rates between the two schedules and the two TDD levels would be computed. A modified Gail and Simon method would be used to test for a qualitative interaction between TDD levels and schedules.

3.1.1.7 Applicant's Results and Statistical Reviewer's Findings/ Comments

3.1.1.7.1 Study Population

Among 724 subjects enrolled between July 13, 2005 to March 13, 2006, 670 were randomized and 662 were treated. Table 3.1.7.1.1 presents the subject disposition.

Table 3.1.7.1.1 Subject Disposition



3.1.1.7.2 Demographic and Baseline Characteristics

Table 3.1.1.7.2.1 presents the demographic characteristics of the randomized subjects.

Table 3.1.1.7.2.1 Demographic Characteristics

	QD (N = 334)			BID (N = 336)		
	100mg TDD N = 167	140mg TDD N = 167	Total N = 334	100mg TDD N = 168	140mg TDD N = 168	Total N = 336
AGE						
N	167	167	334	168	168	336
MEAN	54.6	53.7	54.1	53.3	53.7	53.5
MEDIAN	56.0	54.0	55.0	55.0	54.5	55.0
MIN - MAX	20.0 - 78.0	20.0 - 84.0	20.0 - 84.0	21.0 - 84.0	18.0 - 83.0	18.0 - 84.0
STANDARD DEVIATION	13.6	15.0	14.3	14.6	15.0	14.8
AGE CATERGORIZATION						
< 21	1 (0.6)	3 (1.8)	4 (1.2)	0	3 (1.8)	3 (0.9)
21-45	40 (24.0)	50 (29.9)	90 (26.9)	47 (28.0)	45 (26.8)	92 (27.4)
46-65	80 (47.9)	75 (44.9)	155 (46.4)	83 (49.4)	77 (45.8)	160 (47.6)
66-75	43 (25.7)	26 (15.6)	69 (20.7)	30 (17.9)	34 (20.2)	64 (19.0)
> 75	3 (1.8)	13 (7.8)	16 (4.8)	8 (4.8)	9 (5.4)	17 (5.1)
NOT REPORTED	0	0	0	0	0	0
GENDER (%)						
MALE	84 (50.3)	70 (41.9)	154 (46.1)	85 (50.6)	77 (45.8)	162 (48.2)
FEMALE	83 (49.7)	97 (58.1)	180 (53.9)	83 (49.4)	91 (54.2)	174 (51.8)
NOT REPORTED	0	0	0	0	0	0
RACE (%)						
WHITE	141 (84.4)	125 (74.9)	266 (79.6)	135 (80.4)	142 (84.5)	277 (82.4)
BLACK/AFRICAN AMERICAN	8 (4.8)	9 (5.4)	17 (5.1)	10 (6.0)	10 (6.0)	20 (6.0)
AMERICAN INDIAN/ALASKA NATIVE	0	0	0	1 (0.6)	0	1 (0.3)
ASIAN	12 (7.2)	25 (15.0)	37 (11.1)	17 (10.1)	14 (8.3)	31 (9.2)
NATIVE HAWAIIAN/OTHER PACIFIC ISLANDER	0	0	0	0	0	0
OTHER	5 (3.0)	7 (4.2)	12 (3.6)	4 (2.4)	2 (1.2)	6 (1.8)
NOT REPORTED	1 (0.6)	1 (0.6)	2 (0.6)	1 (0.6)	0	1 (0.3)
ETHNICITY (%)						
HISPANIC/LATINO	5 (3.0)	12 (7.2)	17 (5.1)	5 (3.0)	4 (2.4)	9 (2.7)
NOT HISPANIC/LATINO	53 (31.7)	48 (28.7)	101 (30.2)	45 (26.8)	40 (23.8)	85 (25.3)
NOT REPORTED	109 (65.3)	107 (64.1)	216 (64.7)	118 (70.2)	124 (73.8)	242 (72.0)
PERFORMANCE STATUS (ECOG) (%)						
0	119 (71.3)	115 (68.9)	234 (70.1)	132 (78.6)	111 (66.1)	243 (72.3)
1	44 (26.3)	51 (30.5)	95 (28.4)	33 (19.6)	53 (31.5)	86 (25.6)
2	4 (2.4)	1 (0.6)	5 (1.5)	3 (1.8)	4 (2.4)	7 (2.1)
3	0	0	0	0	0	0
NOT REPORTED	0	0	0	0	0	0
IMATINIB STATUS						
PRIMARY RESISTANCE	75 (44.9)	78 (46.7)	153 (45.8)	88 (52.4)	82 (48.8)	170 (50.6)
ACQUIRED RESISTANCE	49 (29.3)	45 (26.9)	94 (28.1)	36 (21.4)	45 (26.8)	81 (24.1)
INTOLERANCE	43 (25.7)	44 (26.3)	87 (26.0)	44 (26.2)	41 (24.4)	85 (25.3)

Table 3.1.1.7.2.2 presents the baseline hematologic disease status.

Table 3.1.1.7.2.2 Baseline Hematologic Disease Status

	QD (N = 334)			BID (N = 336)		
	100mg TDD N = 167	140mg TDD N = 167	Total N = 334	100mg TDD N = 168	140mg TDD N = 168	Total N = 336
TIME FROM CML TO RANDOMIZATION (MONTHS)						
MEDIAN	55.0	56.0	55.5	50.9	53.0	51.5
MIN - MAX	1.61 - 250.81	0.89 - 227.06	0.89 - 250.81	4.37 - 212.21	1.22 - 245.52	1.22 - 245.52
NUMBER OF SUBJECTS WITH BONE MARROW TRANSPLANT N (%)	10 (6.0)	5 (3.0)	15 (4.5)	13 (7.7)	7 (4.2)	20 (6.0)
NUMBER OF SUBJECTS WITH RADIOTHERAPY N (%)	0	2 (1.2)	2 (0.6)	4 (2.4)	0	4 (1.2)
NUMBER OF SUBJECTS WITH THERAPY AGENT OTHER THAN IMATINIB N (%) (1)	141 (84.4)	147 (88.0)	288 (86.2)	150 (89.3)	147 (87.5)	297 (88.4)
NUMBER OF SUBJECTS WITH CHEMOTHERAPY N (%)	39 (23.4)	41 (24.6)	80 (24.0)	52 (31.0)	43 (25.6)	95 (28.3)
NUMBER OF SUBJECTS WITH INTERFERON USE N (%)	87 (52.1)	93 (55.7)	180 (53.9)	87 (51.8)	82 (48.8)	169 (50.3)
NUMBER OF SUBJECTS WITH HYDROXYUREA OR ANAGRELIDE N (%)	125 (74.9)	131 (78.4)	256 (76.6)	130 (77.4)	130 (77.4)	260 (77.4)

(1) The number of subjects with prior therapy other than imatinib excludes subjects with chemotherapy and /or interferon

Table 3.1.1.7.2.3 presents history of prior imatinib therapy.

Table 3.1.1.7.2.3 Prior Imatinib Therapy

	QD (N = 334)			BID (N = 336)		
	100mg TDD N = 167	140mg TDD N = 167	Total N = 334	100mg TDD N = 168	140mg TDD N = 168	Total N = 336
HIGHEST IMATINIB DOSE (MG)						
< 400	0	0	0	0	0	0
400 - 600	106 (63.5)	111 (66.5)	217 (65.0)	113 (67.3)	111 (66.1)	224 (66.7)
> 600	61 (36.5)	55 (32.9)	116 (34.7)	55 (32.7)	56 (33.3)	111 (33.0)
NOT REPORTED	0	1 (0.6)	1 (0.3)	0	1 (0.6)	1 (0.3)
LENGTH OF IMATINIB THERAPY						
< 1 YEAR	36 (21.6)	39 (23.4)	75 (22.5)	40 (23.8)	37 (22.0)	77 (22.9)
1 - 3 YEARS	55 (32.9)	58 (34.7)	113 (33.8)	68 (40.5)	60 (35.7)	128 (38.1)
> 3 YEARS	76 (45.5)	68 (40.7)	144 (43.1)	60 (35.7)	71 (42.3)	131 (39.0)
NOT REPORTED	0	1 (0.6)	1 (0.3)	0	0	0
BEST HEMATOLOGIC RESPONSE TO IMATINIB						
COMPLETE HEMATOLOGIC RESPONSE	136 (81.4)	138 (82.6)	274 (82.0)	146 (86.9)	141 (83.9)	287 (85.4)
NO RESPONSE TO IMATINIB MESYLATE	28 (16.8)	28 (16.8)	56 (16.8)	17 (10.1)	25 (14.9)	42 (12.5)
NOT REPORTED	3 (1.8)	1 (0.6)	4 (1.2)	5 (3.0)	2 (1.2)	7 (2.1)
BEST CYTOGENETIC RESPONSE TO IMATINIB						
COMPLETE CYTOGENETIC RESPONSE	40 (24.0)	41 (24.6)	81 (24.3)	27 (16.1)	36 (21.4)	63 (18.8)
PARTIAL CYTOGENETIC RESPONSE	36 (21.6)	30 (18.0)	66 (19.8)	38 (22.6)	30 (17.9)	68 (20.2)
MINIMAL CYTOGENETIC RESPONSE	21 (12.6)	17 (10.2)	38 (11.4)	22 (13.1)	15 (8.9)	37 (11.0)
MINOR CYTOGENETIC RESPONSE	15 (9.0)	18 (10.8)	33 (9.9)	13 (7.7)	12 (7.1)	25 (7.4)
NO RESPONSE TO IMATINIB MESYLATE	49 (29.3)	49 (29.3)	98 (29.3)	59 (35.1)	64 (38.1)	123 (36.6)
NOT REPORTED	6 (3.6)	12 (7.2)	18 (5.4)	9 (5.4)	11 (6.5)	20 (6.0)

The baseline imatinib-resistant mutations for the QD and BID schedules were 35% and 36%, and for the 100 mg and 140 mg TDD groups were 38% and 34%, respectively.

3.1.1.7.3 Applicant's Efficacy Analyses

The primary analysis was to compare the MCyR rate between imatinib-resistant subjects in the QD schedule and the BID schedule. The difference in MCyR between the QD and BID schedules in imatinib-resistant subjects was +2.8% with 95% CI (-6.0%, +11.6%), whose lower bound was greater than or equal to -15%. The Gail and Simon test of interaction for MCyR rates between schedule and TDD was 0.50. Table 3.1.1.7.3.1 presents major cytogenetic response rate for imatinib-resistant subjects by schedule.

Table 3.1.1.7.3.1 Major Cytogenetic Response Rate: Imatinib-resistant Subjects by Schedule

	QD N = 247	BID N = 251
MCyR	128 (51.8%)	123 (49.0%)
95% exact CI	45.4% - 58.2%	42.7% - 55.4%
Difference of MCyR	2.8%	
95% CI	-6.0% - 11.6%	

The main secondary objective was to comparea MCyR rate between imatinib-resistant subjects in the 100 mg TDD group and the 140 mg TDD group. The difference in MCyR between the 100 mg TDD and 140 mg TDD in imatinib-resistant subjects was -0.8% with 95% CI (-9.6%, +8.0%), whose lower bound was greater than or equal to -15%. Table 3.1.1.7.3.2 presents major cytogenetic response rate imatinib-resistant subjects by total daily dose.

Table 3.1.1.7.3.2 Major Cytogenetic Response Rate: Imatinib-resistant Subjects by Total Daily Dose

	100 mg TDD N = 248	140 mg TDD N = 250
MCyR	124 (50.0%)	127 (50.8%)
95% exact CI	43.6% - 56.4%	44.4% - 57.2%
Difference of MCyR	-0.8%	
95% CI	-9.6% - 8.0%	

Table 3.1.1.7.3.3 presents cytogenetic and hematologic response rate for all randomized subjects by schedule and by total daily dose.

Table 3.1.1.7.3.3 Cytogenetic and Hematologic Response Rates: All Randomized Subjects by Schedule and by Total Daily Dose

Response	Number (%) of Subjects			
	by schedule		by TDD	
	QD N = 334	BID N = 336	100 mg N = 335	140 mg N = 335
MCyR	191 (57)	183 (54)	188 (56)	186 (56)
CCyR	143 (43)	145 (43)	139 (41)	149 (44)
CHR	293 (88)	300 (89)	304 (91)	289 (86)

Table 3.1.1.7.3.4 presents best cytogenetic response rate for imatinib-resistant subjects by treatment group.

Table 3.1.1.7.3.4 Best Cytogenetic Response: Imatinib-resistant Subjects By Treatment Group

Best Cytogenetic Response	Number (%) of Subjects					
	QD			BID		
	100 mg N = 124	140 mg N = 123	Total N = 247	50 mg N = 124	70 mg N = 127	Total N = 251
MCyR	66 (53)	62 (50)	128 (52)	58 (47)	65 (51)	123 (49)
CCyR	42 (34)	44 (36)	86 (35)	43 (35)	50 (39)	93 (37)
PCyR	24 (19)	18 (15)	42 (17)	15 (12)	15 (12)	30 (12)
minor CyR	11 (9)	9 (7)	20 (8)	8 (6)	9 (7)	17 (7)
minimal CyR	17 (14)	12 (10)	29 (12)	21 (17)	13 (10)	34 (14)
no response	22 (18)	26 (21)	48 (19)	28 (23)	25 (20)	53 (21)
unable to determine	8 (6)	14 (11)	22 (9)	9 (7)	15 (12)	24 (10)

Reviewer's Comments

The clinical study referenced in this submission, according to the applicant, was conducted under IND #66,971. Searching DFS under IND #66,971, no document involving the selected fixed margin -15% used in the primary analysis was found for the protocol of CA180034. As such, whether -15% is a clinical meaningful margin should be based on the clinical judgment and risk / benefit ratio.

The difference in MCyR between the 100 QD and 70 BID schedules in imatinib-resistant subjects was +2.0% with 95% CI (-10.3%, +14.4%), whose lower bound is greater than -15%, suggesting inferior efficacy of 100 QD compared to 70 BID.

3.1.2 Study CA180017

3.1.2.1 Objective

The primary objective was to estimate the rate of major cytogenetic response (MCyR) of dasatinib 70 mg BID and imatinib 800 mg/day (400 mg BID) at 12 weeks in subjects with chronic phase (CP)-chronic myeloid leukemia (CML) resistant to imatinib 400 to 600 mg/day.

3.1.2.2 Study Design

This was an open-label, randomized, non-comparative Phase 2 study of dasatinib and imatinib in subjects with chronic phase CML who were resistant to imatinib 400 to 600 mg/day. Eligible subjects were randomized in a 2-to-1 ratio to either dasatinib 70 mg BID or imatinib 400 mg BID, with continuous daily treatment. Randomization was stratified by site and cytogenetic response on prior imatinib therapy (any prior response). Dasatinib dose modifications were allowed in case of disease progression or lack of response or to manage drug toxicity. No dose escalation was allowed for imatinib. Dose reduction of imatinib to 600 mg/day was allowed, provided the subject had not previously been treated at that dose level. Subjects with lack of response, confirmed disease progression or persistent intolerance despite dose reduction could be crossed over to the alternative treatment after an adequate washout period (2 days for dasatinib, 1 week for imatinib). After crossover, treatment continued until further disease progression or development of intolerable toxicity. Cytogenetic assessment was performed every 12 weeks and at the time of crossover. Hematologic assessment was performed weekly up to 12 weeks and every 3 months thereafter. Database lock for this study was 15-Nov-2006.

3.1.2.3 Efficacy Measures

The primary efficacy endpoint was the MCyR rate at 12 weeks. The MCyR was defined as the rate of CCyR plus the rate of partial cytogenetic response (PCyR). Determination of cytogenetic response was based on the prevalence of Ph+ metaphases among cells in metaphase on a bone marrow sample (aspirate/biopsy). Ideally, at least 20 metaphase cells from a bone marrow sample were evaluated. Cytogenetic response to dasatinib or imatinib included minimal, minor, partial (PCyR), and complete response (CCyR). MCyR was defined as CCyR or PCyR. Response criteria were as outlined below.

	% Ph+ cells in metaphase in bone marrow
Complete Cytogenetic Response (CCyR)	0%
Partial Cytogenetic Response (PCyR)	> 1% to 35%
Minor Cytogenetic Response	> 35% to 65%
Minimal Cytogenetic Response	> 65% to 95%
No Cytogenetic Response	> 95% to 100%

Secondary endpoints included hematologic response and major molecular response at 12 months.

3.1.2.4 Sample Size Considerations

A minimum of 150 subjects were to be randomized in this study in a 2:1 randomization. In the dasatinib group and with a minimum accrual of 100 randomized subjects to that group, the maximum width of the exact 95% confidence interval (CI) of the response rates would be 20%. In the imatinib group and with a minimum accrual of 50 randomized subjects to that group, the maximum width of the exact 95% CI of the response rates would be 29%.

3.1.2.5 Interim Analysis

There was no interim analysis.

3.1.2.6 Statistical Analysis Methods

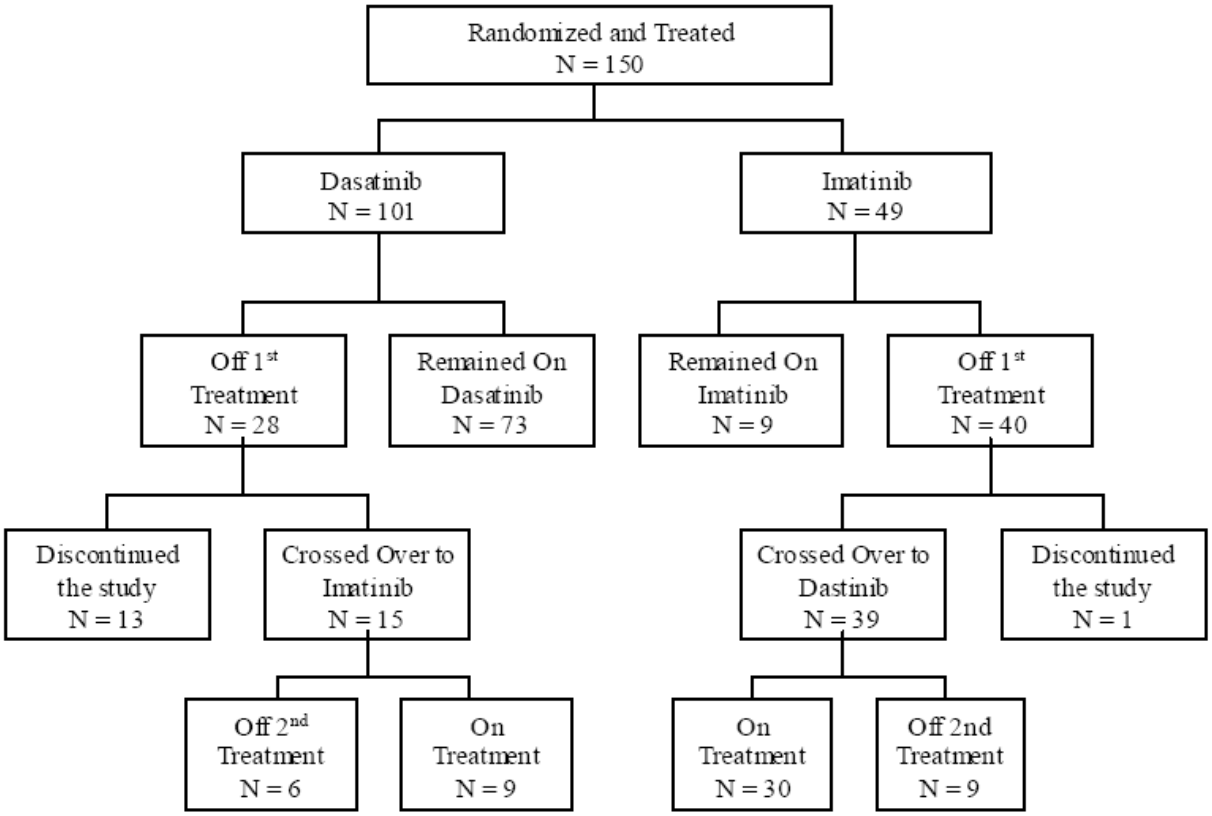
The major cytogenetic response rate at 12 weeks prior to crossover, the major cytogenetic response rate at any time prior to crossover and the CHR rate prior to crossover would be provided along with their 95% exact confidence interval by arm as randomized on the data set of all randomized subjects. The difference between arm of the MCyR rate at 12 weeks and at any time prior to crossover would be provided with its exact 95% CI.

3.1.2.7 Applicant's Results and Statistical Reviewer's Findings/ Comments

3.1.2.7.1 Study Population

A total of 166 subjects enrolled and 16 failed screening. 101 subjects and 49 subjects were randomized and treated with dasatinib and imatinib. Figure 3.1.2.7.1.1 presents the disposition of subjects.

Figure 3.1.2.7.1.1 Disposition of Subjects



3.1.2.7.2 Demographic and Baseline Characteristics

Table 3.1.2.7.2.1 presents patient demographic characteristics at baseline.

Table 3.1.2.7.2.1 Patient Demographic Characteristics at Baseline
All Randomized Patients

	DASATINIB N = 101	IMATINIB N = 49	Total N = 150
AGE			
N	101	49	150
MEAN	51	50	51
MEDIAN	51	51	51
MIN - MAX	24 - 85	24 - 80	24 - 85
STANDARD DEVIATION	13.6	13.6	13.5
AGE CATERGORIZATION (%)			
21-45	36 (35.6)	15 (30.6)	51 (34.0)
46-65	48 (47.5)	28 (57.1)	76 (50.7)
66-75	13 (12.9)	5 (10.2)	18 (12.0)
> 75	4 (4.0)	1 (2.0)	5 (3.3)
GENDER (%)			
MALE	53 (52.5)	22 (44.9)	75 (50.0)
FEMALE	48 (47.5)	27 (55.1)	75 (50.0)
RACE (%)			
WHITE	87 (86.1)	43 (87.8)	130 (86.7)
BLACK/AFRICAN AMERICAN	2 (2.0)	1 (2.0)	3 (2.0)
ASIAN	6 (5.9)	3 (6.1)	9 (6.0)
OTHER	6 (5.9)	2 (4.1)	8 (5.3)
PERFORMANCE STATUS (ECOG) (%)			
0	71 (70.3)	34 (69.4)	105 (70.0)
1	27 (26.7)	12 (24.5)	39 (26.0)
NOT REPORTED	3 (3.0)	3 (6.1)	6 (4.0)

Table 3.1.2.7.2.2 presents disease history.

Table 3.1.2.7.2.2 Disease History
All Randomized Patients

	DASATINIB N = 101	IMATINIB N = 49	Total N = 150
TIME FROM INITIAL CML DIAGNOSIS TO RANDOMIZATION (MONTHS)			
MEDIAN	64.1	51.8	58.8
MIN - MAX	5.6 - 166.2	13.8 - 132.6	5.6 - 166.2
NUMBER OF SUBJECTS WITH BONE MARROW TRANSPLANT N (%)	7 (6.9)	2 (4.1)	9 (6.0)
NUMBER OF SUBJECTS WITH RADIOTHERAPY N (%)	2 (2.0)	0	2 (1.3)
NUMBER OF SUBJECTS WITH THERAPY AGENT OTHER THAN IMATINIB N (%) (1)	101 (100.0)	49 (100.0)	150 (100.0)
NUMBER OF SUBJECTS WITH CHEMOTHERAPY N (%)	39 (38.6)	18 (36.7)	57 (38.0)
NUMBER OF SUBJECTS WITH INTERFERON USE N (%)	74 (73.3)	33 (67.3)	107 (71.3)
NUMBER OF SUBJECTS WITH HYDROXYUREA OR ANAGRELIDE N (%)	97 (96.0)	46 (93.9)	143 (95.3)

Table 3.1.2.7.2.3 presents prior imatinib therapy.

Table 3.1.2.7.2.3 Prior Imatinib Therapy
All Randomized Patients

	DASATINIB N = 101	IMATINIB N = 49	Total N = 150
HIGHEST IMATINIB DOSE (MG)			
400	36 (35.6)	14 (28.6)	50 (33.3)
500	2 (2.0)	1 (2.0)	3 (2.0)
600	62 (61.4)	34 (69.4)	96 (64.0)
800	1 (1.0)	0	1 (0.7)
LENGTH OF IMATINIB THERAPY			
< 1 YEAR	12 (11.9)	5 (10.2)	17 (11.3)
1 - 3 YEARS	44 (43.6)	29 (59.2)	73 (48.7)
> 3 YEARS	45 (44.6)	15 (30.6)	60 (40.0)
BEST HEMATOLOGIC RESPONSE TO IMATINIB			
COMPLETE HEMATOLOGIC RESPONSE	93 (92.1)	47 (95.9)	140 (93.3)
STABLE	7 (6.9)	2 (4.1)	9 (6.0)
PROGRESSION	0	0	0
UNABLE TO DETERMINE	1 (1.0)	0	1 (0.7)
BEST CYTOGENETIC RESPONSE TO IMATINIB			
COMPLETE CYTOGENETIC RESPONSE	15 (14.9)	4 (8.2)	19 (12.7)
PARTIAL CYTOGENETIC RESPONSE	13 (12.9)	10 (20.4)	23 (15.3)
MINIMAL CYTOGENETIC RESPONSE	24 (23.8)	14 (28.6)	38 (25.3)
MINOR CYTOGENETIC RESPONSE	10 (9.9)	6 (12.2)	16 (10.7)
STABLE	37 (36.6)	13 (26.5)	50 (33.3)
PROGRESSION	0	1 (2.0)	1 (0.7)
UNABLE TO DETERMINE	2 (2.0)	1 (2.0)	3 (2.0)

3.1.2.7.3 Applicant's Efficacy Analyses

The MCyR rate at 12 weeks was 36% in the dasatinib group and 29% in the imatinib group. The difference in MCyR rates was 7% (95% CI - 9.8, 22.2). Table 3.1.2.7.3.1 presents the primary analysis results.

Table 3.1.2.7.3.1 MCyR Rate at 12 Weeks prior to Crossover

	Dasatinib N=101	Imatinib N=49
Major Cytogenetic Response at 12wks	36 (35.6%)	14 (28.6%)
95% exact CI	26.4% , 45.8%	16.6% , 43.3%
Difference of MCyR at 12 weeks	7.1%	
95% exact CI	-9.8% , 22.2%	

The CCyR rate at 12 weeks was higher for the dasatinib group compared with the imatinib group (22% vs 8%). The difference in CCyR rates was 14% (95% CI 0.6, 24.8). Table 3.1.2.7.3.2 presents the detailed response results.

Table 3.1.2.7.3.2 Cytogenetic Response at 12 Weeks prior to Crossover
All Randomized Patients

Treatment Group	DASATINIB N = 101	IMATINIB N = 49
Cytogenetic Response at 12 weeks		
Complete (0%)	22 (21.8)	4 (8.2)
Partial (>0% - 35%)	14 (13.9)	10 (20.4)
Minor (>35% - 65%)	5 (5.0)	3 (6.1)
Minimal (>65% - 95%)	18 (17.8)	6 (12.2)
No Response (>95% - 100%)	33 (32.7)	22 (44.9)
Unable to determine	9 (8.9)	4 (8.2)

Reviewer's Comments

The applicant's primary objective was to estimate the rate of major cytogenetic response (MCyR) of dasatinib 70 mg BID and imatinib 800 mg/day (400 mg BID) at 12 weeks. A superiority or a non-inferiority comparisons were not planned.

3.2 Evaluation of Safety

Please refer to Clinical Review of this application for complete safety evaluation.

4. Findings in Special/Subgroup Populations

4.1 Gender, Race, and Age

Table 4.1.1 presents the MCyR rate by age, race and gender subgroups for study CA180034.

Table 4.1.1 CA180034: MCyR rate (#/total (%))

Subgroup	Category	100 mg QD N = 124	140 mg QD N = 123	50 mg BID N = 124	70 mg BID N = 127
age	< 65	46 / 84 (55)	53 / 88 (60)	50 / 96 (52)	51 / 90 (57)
	≥ 65	20 / 39 (51)	9 / 31 (29)	8 / 27 (30)	14 / 36 (39)
race	white	57 / 102 (56)	44 / 92 (48)	50 / 102 (49)	55 / 107 (51)
	other	9 / 21 (43)	18 / 27 (67)	8 / 21 (38)	10 / 19 (53)
gender	female	22 / 51 (43)	33 / 60 (55)	26 / 57 (46)	33 / 66 (50)
	male	44 / 72 (61)	29 / 59 (49)	32 / 66 (48)	32 / 60 (53)

Table 4.1.2 presents the MCyR rates by age, race and gender subgroups for study CA180017.

Table 4.1.2 CA180017: MCyR rate (#/total (%))

Subgroup	Category	Dasatinib N=101	Imatinib N=49
age	< 65	29 / 82 (35)	12 / 40 (30)
	≥ 65	7 / 19 (37)	2 / 9 (22)
race	white	34 / 87 (39)	12 / 43 (18)
	other	2 / 14 (14)	2 / 6 (33)
gender	female	14 / 48 (29)	6 / 27 (22)
	male	22 / 53 (42)	8 / 22 (36)

4.2 Other Special/Subgroup Populations

There was no analysis performed on other subgroups.

5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

In Study CA180034, the primary analysis was to compare a MCyR rate between imatinib-resistant subjects in the QD schedule and the BID schedule. The MCyR rate was 51.8% (95% CI 45.4% - 58.2%) for QD and 49.0% (95% CI 42.7% - 55.4%) for BID. The difference in MCyR between the QD and BID schedules in imatinib-resistant subjects was +2.8% with 95% CI (-6.0%, +11.6%), whose lower bound was greater than or equal to -15%. Whether the selected fixed margin -15% used in the non-inferiority analysis was clinically meaningful should be based on the clinical judgment and risk and benefit ratio.

In Study CA180017, the MCyR rate at 12 weeks was 36% (95% CI 26.4% - 45.8%) in the dasatinib group and 29% (95% CI 16.6% - 43.3%) in the imatinib group.

5.2 Conclusions and Recommendations

The applicant submitted the data and analyses of two trials, CA180034 and CA180017 (mainly for updating the report submitted in the initial NDA), to seek a change in the dose and administration schedule for dasatinib in the treatment of subjects with chronic phase CML. The data and analyses in this supplemental NDA demonstrated that the efficacy of dasatinib when administered QD was similar to that administered BID in the treatment of subjects with chronic phase CML and support a change in the dose and administration schedule for dasatinib in the treatment of subjects with chronic phase CML.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-986/S001 & 002

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	21-986
Submission Date:	10 May 2007
Brand Name:	Sprycel®
Generic Name:	Dasatinib (BMS 354825)
Formulation:	20 mg, 50 mg, and 70 mg film coated tablets.
OCP Reviewer:	Julie M. Bullock, Pharm.D.
OCP Team Leader:	Brian Booth, Ph.D.
OCP Division:	Division of Clinical Pharmacology V
ORM Division:	Division of Drug Oncology Products
Sponsor:	Bristol Meyers Squibb
Submission Type; Code:	sNDA; SE2; 001
Dosing regimen:	100 mg QD
Indication:	NDA 21-986: chronic myeloid leukemia (CML)

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1 EXECUTIVE SUMMARY

Sprycel® (dasatinib) is a small molecule inhibitor of multiple oncogenic kinases. Dasatinib has been previously approved on June 28, 2006 for the treatment of adults with chronic myeloid leukemia (NDA 21-986) or Philadelphia chromosome-positive acute lymphoblastic leukemia (NDA 22-072) with resistance or intolerance to prior therapy including imatinib.

The current submission is a supplemental NDA for dasatinib. It includes data from studies CA180017 and CA180034 to support a 100 mg QD dose for the treatment of chronic phase CML and to provide data related to post-marketing commitments #5 and #7:

5. You have agreed to submit the complete study report (24 month follow-up) and data from the study, CA-180-017, a randomized, open-label multicenter study of dasatinib (BMS-354825) versus Imatinib Mesylate (Gleevec, Glivec) 800 mg/d in subjects with Chronic Phase Philadelphia Chromosome Positive Chronic Myeloid Leukemia who have disease that is resistant to Imatinib Mesylate at a Dose of 400 - 600 mg/d.

   Protocol Submission: 11/2004
   Study Start: 02/2005
   Final Report Submission: 12/2008

7. You have agreed to submit the completed study report (24 month follow-up) and data from the study, CA-180-034, a randomized, two-by-two, open-label study of dasatinib (BMS-354825) in subjects with Chronic Phase Philadelphia Chromosome Positive Chronic Myeloid Leukemia resistant to or intolerant of Imatinib Mesylate.

   Protocol Submission: 04/2005
   Study Start: 07/2005
   Final Report Submission: 06/2009

At the time of submission the sponsor did not provide any new pharmacokinetic data. Since the AUC of dasatinib was liner following BID and QD doses ranging from 25 - 120 mg the addition of a 100 mg QD dose is appropriate from a clinical pharmacology standpoint.

This review will focus only on the Physician's Labeling Rule (PLR) conversion.

1.1 RECOMMENDATIONS

Please see labeling below. No action is indicated.

Signatures

Julie M. Bullock, Pharm.D.	Brian Booth, Ph.D.
Reviewer	Deputy Division Director & Acting Team Leader
Division of Clinical Pharmacology 5	Division of Clinical Pharmacology 5

Cc: DDOP: CSO - S Thomas; MTL - A Farrell; MO - M Ning
DCP-5: Reviewer - J Bullock, DDD & Acting TL - B Booth; DD - A Rahman

1.2 LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are noted.

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------DRUG INTERACTIONS----------

- *CYP3A4 Inhibitors*: May increase dasatinib drug levels and should be avoided. If coadministration cannot be avoided, monitor closely and consider reducing SPRYCEL dose. (2.1, 7.1)
- *CYP3A4 Inducers* May decrease dasatinib drug levels. If coadministration cannot be avoided, consider increasing SPRYCEL dose. (2.1, 7.2)
- *Antacids* May decrease dasatinib drug levels. Avoid simultaneous administration. If needed, administer the antacid at least 2 hours prior to or 2 hours after the dose of SPRYCEL. (7.2)
- *H_2 Antagonists/Proton Pump Inhibitors* May decrease dasatinib drug levels. Consider antacids in place of H_2 antagonists or proton pump inhibitors. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- *Hepatic Impairment* Use SPRYCEL with caution in patients with hepatic impairment. (8.6)

2.1 Dose Modification

Concomitant Strong CYP3A4 inducers: The use of concomitant strong CYP3A4 inducers may decrease dasatinib plasma concentrations and should be avoided (eg, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital). St. John's Wort may decrease dasatinib plasma concentrations unpredictably and should be avoided. If patients must be coadministered a strong CYP3A4 inducer, based on pharmacokinetic studies, a SPRYCEL dose increase should be considered. If the dose of SPRYCEL is increased, the patient should be monitored carefully for toxicity *[see Drug Interactions (7.2)]*.

Concomitant Strong CYP3A4 inhibitors: CYP3A4 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) may increase dasatinib plasma concentrations. Grapefruit juice may also increase plasma concentrations of dasatinib and should be avoided.

Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. If SPRYCEL must be administered with a strong CYP3A4 inhibitor, a dose decrease to 20 mg daily should be considered. If 20 mg/day is not tolerated, either the strong CYP3A4 inhibitor must be discontinued, or SPRYCEL should be stopped until treatment with the inhibitor has ceased. When the strong inhibitor is discontinued, a washout period of approximately 1 week should be allowed before the SPRYCEL dose is increased. [See Drug Interactions (7.1)].

7 DRUG INTERACTIONS

7.1 Drugs That May Increase Dasatinib Plasma Concentrations

CYP3A4 Inhibitors: Dasatinib is a CYP3A4 substrate. In a study of 18 patients with solid tumors, 20-mg SPRYCEL once daily coadministered with 200 mg of ketoconazole twice daily increased the dasatinib C_{max} and AUC by four- and five-fold, respectively. Concomitant use of SPRYCEL and drugs that inhibit CYP3A4 may increase exposure to dasatinib and should be avoided. In patients receiving treatment with SPRYCEL, close monitoring for toxicity and a SPRYCEL dose reduction should be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided *[see Dosage and Administration (2.1)]*.

7.2 Drugs That May Decrease Dasatinib Plasma Concentrations

CYP3A4 Inducers: When a single morning dose of SPRYCEL was administered following 8 days of continuous evening administration of 600 mg of rifampin, a potent CYP3A4 inducer, the mean C_{max} and AUC of dasatinib were decreased by 81% and 82%, respectively. Alternative agents with less enzyme induction potential should be considered. If SPRYCEL must be administered with a CYP3A4 inducer, a dose increase in SPRYCEL should be considered *[see Dosage and Administration (2.1)]*.

Antacids: Nonclinical data demonstrate that the solubility of dasatinib is pH dependent. In a study of 24 healthy subjects, administration of 30 mL of aluminum hydroxide/magnesium hydroxide 2 hours prior to a single 50-mg dose of SPRYCEL was associated with no relevant change in dasatinib AUC; however, the dasatinib C_{max} increased 26%. When 30 mL of aluminum hydroxide/magnesium hydroxide was administered to the same subjects concomitantly with a 50-mg dose of SPRYCEL, a 55% reduction in dasatinib AUC and a 58% reduction in C_{max} were observed. Simultaneous administration of SPRYCEL with antacids should be avoided. If antacid therapy is needed, the antacid dose should be administered at least 2 hours prior to or 2 hours after the dose of SPRYCEL.

H_2 Antagonists/Proton Pump Inhibitors: Long-term suppression of gastric acid secretion by H_2 antagonists or proton pump inhibitors (eg, famotidine and omeprazole) is likely to reduce dasatinib exposure. In a study of 24 healthy subjects, administration of a single 50-mg dose of SPRYCEL 10 hours following famotidine reduced the AUC and C_{max} of dasatinib by 61% and

63%, respectively. The concomitant use of H_2 antagonists or proton pump inhibitors with SPRYCEL is not recommended. The use of antacids should be considered in place of H_2 antagonists or proton pump inhibitors in patients receiving SPRYCEL therapy.

7.3 Drugs That May Have Their Plasma Concentration Altered By Dasatinib

CYP3A4 Substrates: Single-dose data from a study of 54 healthy subjects indicate that the mean C_{max} and AUC of simvastatin, a CYP3A4 substrate, were increased by 37% and 20%, respectively, when simvastatin was administered in combination with a single 100-mg dose of SPRYCEL. Therefore, CYP3A4 substrates known to have a narrow therapeutic index such as alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, or ergot alkaloids (ergotamine, dihydroergotamine) should be administered with caution in patients receiving SPRYCEL.

8 USE IN SPECIFIC POPULATIONS

8.6 Hepatic Impairment

There are currently no clinical studies with SPRYCEL in patients with impaired liver function (clinical studies have excluded patients with ALT or AST >2.5 times the upper limit of the normal range or total bilirubin >2 times the upper limit of the normal range). Metabolism of dasatinib is mainly hepatic. Caution is recommended in patients with hepatic impairment.

8.7 Renal Impairment

There are currently no clinical studies with SPRYCEL in patients with impaired renal function (b) (4) [redacted] Less than 4% of SPYCEL and its metabolites are excreted via the kidney.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Absorption

Maximum plasma concentrations (C_{max}) of dasatinib are observed between 0.5 and 6 hours (T_{max}) following oral administration. Dasatinib exhibits dose proportional increases in AUC and linear elimination characteristics over the dose range of 15 mg to 240 mg/day. The overall mean terminal half-life of dasatinib is 3–5 hours.

Data from a study of 54 healthy subjects administered a single, 100-mg dose of dasatinib 30 minutes following consumption of a high-fat meal resulted in a 14% increase in the mean AUC of dasatinib. The observed food effects were not clinically relevant.

Distribution

In patients, dasatinib has an apparent volume of distribution of 2505 L, suggesting that the drug is extensively distributed in the extravascular space. Binding of dasatinib and its active metabolite to human plasma proteins *in vitro* was approximately 96% and 93%, respectively, with no concentration dependence over the range of 100–500 ng/mL.

Metabolism

Dasatinib is extensively metabolized in humans, primarily by the cytochrome P450 enzyme 3A4. CYP3A4 was the primary enzyme responsible for the formation of the active metabolite. Flavin-containing monooxygenase 3 (FMO-3) and uridine diphosphate-glucuronosyltransferase (UGT) enzymes are also involved in the formation of dasatinib metabolites. In human liver microsomes, dasatinib was a weak time-dependent inhibitor of CYP3A4.

The exposure of the active metabolite, which is equipotent to dasatinib, represents approximately 5% of the dasatinib AUC. This indicates that the active metabolite of dasatinib is unlikely to play a major role in the observed pharmacology of the drug. Dasatinib also had several other inactive oxidative metabolites.

Dasatinib is a time-dependent inhibitor of CYP3A4. At clinically relevant concentrations, dasatinib does not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, or 2E1. Dasatinib is not an inducer of human CYP enzymes.

Elimination

Elimination is primarily via the feces. Following a single oral dose of [^{14}C]-labeled dasatinib, approximately 4% and 85% of the administered radioactivity was recovered in the urine and feces, respectively, within 10 days. Unchanged dasatinib accounted for 0.1% and 19% of the administered dose in urine and feces, respectively, with the remainder of the dose being metabolites.

Effects of Age and Gender

Pharmacokinetic analyses of demographic data indicate that there are no clinically relevant effects of age and gender on the pharmacokinetics of dasatinib.

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/s/

Julie Bullock
11/5/2007 01:33:48 PM
BIOPHARMACEUTICS

Brian Booth
11/7/2007 08:51:04 AM
BIOPHARMACEUTICS

Clinical Pharmacology - NDA Filing Memo

NDA:	**21-986**
Compound:	**Sprycel® (dasatinib)**
Sponsor:	**Bristol-Myers Squibb**
Submission Date:	**10 May 2007**
Filing Date:	**24 July 2007**
Reviewer:	**Julie M. Bullock, Pharm.D.**

Background:

Dasatinib (BMS-354825) is a oral inhibitor of multiple oncogenic kinases which was approved on June 28, 2007 for the treatment of subjects with chronic phase CML, advanced (accelerated and blast) phase CML, or Ph+ ALL who are resistant or intolerant to imatinib. The recommended dose for dasatinib of 70 mg BID was based on one Phase 1 study and five Phase 2 studies showing efficacy and manageable toxicity in subjects with CML or Ph+ ALL who were resistant or intolerant to imatinib.

The current application is based upon one Phase 3 study (CA180034) comparing the efficacy and safety of dasatinib administered QD versus BID in subjects with chronic phase CML. Efficacy results from the randomized Phase 2 study (CA180017) in 150 subjects with chronic phase CML with a median follow-up of 15 months are also presented as an update to the report submitted in the initial application.

No new information regarding clinical pharmacology or biopharmaceutics was submitted with the submission dated May 10, 2007. Sparse pharmacokinetic samples were obtained in study CA180017 on Day 8 at predose, between 30 min-3 hours, between 5-8 hours and at 12 hours post dose. Pharmacokinetics was also assessed in study CA180034. The sponsor mentions in the PK results section of the study reports that "the plasma PK of dasatinib will be included in a separate PK report and used in conjunction with samples from other clinical studies as part of a population PK assessment", however no timeline was given on when this would be submitted.

Comment:

When can we expect the submission containing the pharmacokinetic results, population PK report and pharmacokinetic data from studies CA180034 and CA180017?

Action:

Please inquire as to when the items in the above comment will be submitted.

Signatures:

Julie M. Bullock, Pharm.D.	Brian Booth, Ph.D.
Reviewer	Deputy Div Director & Acting Team Leader
Division of Clinical Pharmacology 5	Division of Clinical Pharmacology 5

Cc: DDOP: CSO - **S Thomas;** MTL - **A Farrell**; MO - **M Ning**
DCP-5: Reviewer - **J Bullock;** Deputy DD & Acting TL - **B Booth;**
DD - **A Rahman**

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/s/

Julie Bullock
7/20/2007 03:46:05 PM
BIOPHARMACEUTICS

Brian Booth
7/31/2007 01:26:03 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-986/S001 & 002

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-986 SUPPL # S-001 HFD # 150

Trade Name SPRYCEL®

Generic Name Dasatinib

Applicant Name Bristol Myers Squibb

Approval Date, If Known 11/6/07

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE2

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-986 SPRYCEL® (dasatinib) Tablets

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

INVESTIGATION #1: CA 180034: A Randomized Two by Two, Multi-Center, 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 Subjects With Chronic Phase Philadelphia Chromosome Positive or BCR-ABL Positive Chronic Myelogenous Leukemia Who are Resistant or Intolerant to Imatinib Mesylate

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

INVESTIGATION #1: CA 180034: A Randomized Two by Two, Multi-Center, 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 Subjects With Chronic Phase Philadelphia Chromosome Positive or BCR-ABL Positive Chronic Myelogenous Leukemia Who are Resistant or Intolerant to Imatinib Mesylate

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 66,971	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Milinda Vialpando
Title: Regulatory Project Manager
Date: 11/2/07

Name of Office/Division Director signing form: Robert Justice, M.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Robert Justice

11/9/2007 01:54:21 PM

EXCLUSIVITY SUMMARY

NDA # 21-986 SUPPL # S-002 HFD # 150

Trade Name SPRYCEL®

Generic Name Dasatinib

Applicant Name Bristol Myers Squibb

Approval Date, If Known 11/6/07

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-986 SPRYCEL® (dasatinib) Tablets

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

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IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

INVESTIGATION #1: CA 180017: A Randomized Multicenter Open Label Study of BMS-354825 vs Imatinib Mesylate (Gleevec®, Glivec®) 800 mg/day in Subjects with Chronic Phase Philadelphia Chromosome-positive Chronic Myeloid Leukemia Who Have Disease That Is Resistant to Imatinib at a Dose of 400 - 600 mg/day.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

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INVESTIGATION #1: CA 180017: A Randomized Multicenter Open Label Study of BMS-354825 vs Imatinib Mesylate (Gleevec®, Glivec®) 800 mg/day in Subjects with Chronic Phase Philadelphia Chromosome-positive Chronic Myeloid Leukemia Who Have Disease That Is Resistant to Imatinib at a Dose of 400 - 600 mg/day

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 66,971	YES ☒	! NO ☐
		! Explain:
Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Milinda Vialpando
Title: Regulatory Project Manager
Date: 11/2/07

Name of Office/Division Director signing form: Robert Justice, M.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Robert Justice

11/9/2007 01:56:08 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # :21-986 **Supplement Type (e.g. SE5):** SE2 **Supplement Number:** 001

Stamp Date: May 10, 2007 **PDUFA Goal Date:** November 11, 2007

HFD 150 **Trade and generic names/dosage form:** SPRYCEL® (dasatinib) Tablets

Applicant: Bristol-Myers Squibb Company **Therapeutic Class:** 5010100

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- ☑ **Yes. Please proceed to the next question.**
- **No. PREA does not apply. Skip to signature block.**

**** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.***

Indication(s) *previously approved* (please complete this section for supplements only): The treatment of adults with chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib.

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: Treatment of adults in chronic phase (CML).

Is this an orphan indication?

- ☑ **PREA does not apply. Skip to signature block.**
- ☐ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ❑ **No: Please check all that apply: Partial Waiver Deferred Completed**

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____
Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- ❑ **Yes. PREA does not apply. Skip to signature block.**
- ❑ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**
- ❑ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager
Sharon Thomas

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sharon Thomas

8/23/2007 02:47:57 PM

NDA NO. 21-986

SPRYCEL (DASATINIB)

CERTIFICATION: DEBARRED PERSONS

As required by Section 306(k)(1) of the Federal Food, Drug and Cosmetics Act, Bristol-Myers Squibb Company certifies that it has not used and will not use in any capacity the services of any person listed as debarred under Section 306 (a) or (b) of the Federal Food, Drug and Cosmetics Act in connection with this Application.

Meenal Pai, PharmD
Manager, Global Regulatory Science
Bristol-Myers Squibb Company

April 17, 2007
Certification Date

ACTION PACKAGE CHECKLIST

Application Information			
BLA # NDA # 21-986	BLA STN# NDA Supplement # SE2-001	If NDA, Efficacy Supplement Type SE2	
Proprietary Name: SPRYCEL Established Name: dasatinib Dosage Form: Tablets 20 mg, 50 mg, 70 mg		Applicant: Bristol Myers Squibb	
RPM: Milinda Vialpando		Division: DDOP	Phone # 301-796-1444

NDAs:	505(b)(2) NDAs and 505(b)(2) NDA supplements:
NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.** ☐ Confirmed ☐ Corrected Date:

❖ User Fee Goal Date ❖ Action Goal Date (if different)	11/11/07
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	☐ Requested in AP letter ☒ Received and reviewed 8/15/07

❖ Application Characteristics

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review
☐ CMA Pilot 1
☐ CMA Pilot 2

☒ Orphan drug designation

NDAs: Subpart H
☒ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes ☐ No
• OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other - Burst

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	☒ Included
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified
• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's	☐ Yes ☐ No

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (3).*

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	Clin TL - Dep Div Dir -
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	5/10/07
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	5/10/07
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	
❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	☐ DMETS ☐ DSRCS ☒ DDMAC 8/15/07 ☐ SEALD ☐ Other reviews ☐ Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	
❖ Pediatric Page (all actions)	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	☒ Verified, statement is acceptable
❖ Postmarketing Commitment Studies	☐ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	In previous approval letter. No new PMCs (PMC #7 from original letter is now required).
• Incoming submission documenting commitment	
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	Included
❖ Internal memoranda, telecons, email, etc.	Included
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	11/1/07
• Pre-NDA/BLA meeting *(indicate date)*	☒ No mtg
• EOP2 meeting *(indicate date)*	☒ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting	☒ No AC meeting
• Date of Meeting	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	8/16/07
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	☒ None
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☐ No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• ☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	8/16/07
• ☐ Review & FONSI *(indicate date of review)*	
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	☐ Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: ☐ Acceptable ☐ Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☒ Not yet requested ☐ Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	☐ None requested
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	☒ None
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	☒ Not needed
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	Not needed
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	☒ Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested
• Clinical Studies	
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) *(indicate date for each review)*	☐ None 10/25/07
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 11/5/07

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

From: Vialpando, Milinda
To: "meenal.pai@bms.com";
Subject: RE: follow up- CA180051question regarding submission of SPRYCEL postmarketing commitments (PMCs) and) acknowledgement letter for the full approval sNDA: NDA 21-986, 22-072
Date: Tuesday, November 25, 2008 2:14:13 PM

Hi Meenal,

It is acceptable to submit the final study report for CA180051 (PMC #8 for NDA 21-986), datasets and proposed US PI .

Thanks for your cooperation.
Milinda

From: meenal.pai@bms.com [mailto:meenal.pai@bms.com]
Sent: Wednesday, November 12, 2008 1:01 PM
To: Vialpando, Milinda
Subject: follow up- CA180051question regarding submission of SPRYCEL postmarketing commitments (PMCs) and)acknowledgement letter for the full approval sNDA: NDA 21-986, 22-072
Importance: High

Dear Milinda,
Thanks for the filing letter. I would like to follow up urgently on 2 items below:

- FDA acceptance of BMS proposal to submit the final study report for CA180051 (PMC #8 for NDA 21-986 and PMC #2 for NDA 22-072), datasets and proposed US PI
- acknowledgement letter for the full approval sNDA: NDA 21-986, 22-072 submitted on 31 July 2008 stating the review granted for the sNDA

I look forward to hearing from you soon.

Sincerely,
Meenal Pai, Pharm.D.
Associate Director, Global Regulatory Science
Bristol-Myers Squibb Company
Tel no.: 203-677-6941
Fax: 203-677-3818

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Milinda Vialpando
11/25/2008 02:29:08 PM
CSO

Milinda Vialpando
11/25/2008 02:29:34 PM
CSO

From:	Vialpando, Milinda
To:	"meenal.pai@bms.com";
CC:	"Marie-Laure Papi";
Subject:	Response needed for sNDA21-986 Sprycel
Date:	Friday, October 12, 2007 10:46:26 AM
Attachments:	

Meenal,

Please see question from the clinical review and send response to me right away.

Re: Toxicity of overdosed dasatinib 280 mg qd x 7 days,

sNDA 021986

1. The toxicity of the overdose of dasatinib (280 mg QD x 7 days) was not clearly described in your response to the FDA recent inquiry concerning Section 10 (*overdosage*). Two study patients were reported to have had that exposure. Subject CA180035-128-35304 developed pulmonary tract hemorrhage with Grade 4 thrombocytopenia one week after the drug was stopped, and deceased four days later due to the hemorrhage. The other subject CA180013-57-13379 displayed severe bone marrow suppression two weeks after the ingestion and had a group of adverse events suggestive of Grade 3 pneumonitis. Please provide their case report forms or relevant medical documents that would help understand the toxicity of this overdose in these two patients.

Thanks,

Milinda F. Vialpando
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products, FDA
10903 New Hampshire Avenue
Building 22, Room 2133
Silver Spring, MD 20993
Tel: 301-796-1444
Fax: 301-796-9845

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/s/

Milinda Vialpando
10/12/2007 10:50:40 AM
CSO

From:	Vialpando, Milinda
To:	"meenal.pai@bms.com"; "Marie-Laure Papi";
CC:	
Subject:	Information needed for sNDA 21-986, Sprycel, Safety review questions
Date:	Friday, October 05, 2007 11:09:52 AM
Attachments:	Response to FDA query of Sep 14,2007.pdf

Meenal and Marie-Laure,

Please see the safety review questions below and send the responses right away. Also, can you please send the word document for the attached .pdf file?

Feel free to contact me if you have any questions.

sNDA 021986

1. There are considerable differences in the rate of dasatinib discontinuation due to adverse reactions between your proposed label *(Section 6.1)* and the medical reviewer's evaluation. Please specify how you generated your discontinuation rates for the four different disease phases as well as in patients treated with dasatinib 100 mg QD vs 70 mg BID.

2. Similar to Question one, the discontinuation rates the reviewer tabulated based on AETRT.xpt are different from those based on NEWAEGRP.xpt. Please clarify what are the differences between AETRT.xpt and NEWAEGRP.xpt and which one is more comprehensive and reliable.

3. For Study CA180017, the updated AETRT.xpt, NEWAEGRP.xpt, and LB17.xpt do not include the information

about the patients treated with imatinib prior to cross-over. The reviewer could not evaluate the updated incidences of the imatinib-associated adverse events and laboratory abnormalities as shown in your updated label. Please clarify what datasets were used for updating the imatinib-associated adverse events and laboratory abnormalities prior to cross over.

Thank You,

Milinda F. Vialpando
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products, FDA
10903 New Hampshire Avenue
Building 22, Room 2133
Silver Spring, MD 20993
Tel: 301-796-1444
Fax: 301-796-9845

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/s/

Milinda Vialpando
10/5/2007 11:33:48 AM
CSO

From:	Vialpando, Milinda
To:	"meenal.pai@bms.com"; "Marie-Laure Papi";
CC:	
Subject:	Labeling Information request: sNDA 21-986 (Sprycel, dasatinib)
Date:	Tuesday, September 04, 2007 5:30:42 PM
Attachments:	

Meenal and Marie-Laure,

Please see the information request below related to the Sprycel (dasatinib) labeling review in Section 6.1 Clinical Studies Experience, page 7. The submitted file you provided was named Proposed.doc.

You stated that pooled safety data from the overall population of 2182 dasatinib-treated subjects were used for the dasatinib safety analyses as shown in Tables 2 and 5 of the proposed dasatinib label. Please clarify which trials you included for the tabulations. Your dataset *AETRT* included 8 trials with a total of 2133 subjects, of which 599 were from an ongoing study CA180035. No information was provided about that study and the treatment exposure to dasatinib in those 599 subjects. Prior to further analysis or confirmation of your tabulated safety information, it is necessary to address the appropriateness of your study inclusion of the dataset you were based on for the overall safety evaluation.

Please contact me if you have any questions.

Thank You,

Milinda F. Vialpando
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products, FDA
10903 New Hampshire Avenue
Building 22, Room 2133
Silver Spring, MD 20993
Tel: 301-796-1444
Fax: 301-796-9845

APPEARS THIS WAY ON ORIGINAL

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/s/

Milinda Vialpando
9/4/2007 05:39:40 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-986/ S-001, S-002

PRIOR APPROVAL SUPPLEMENT

Bristol-Myers Squibb Company
5 Research Parkway
P.O. Box 5100, Mailstop 3SIG-3021
Wallingford, CT 06492

Attention: Meenal Pai, Pharm.D.
Manager, Global Regulatory Sciences

Dear Ms. Pai:

We have received your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: SPRYCEL® (dasatinib, BMS-354825) tablets.

Review Priority Classification: Priority

Date of Application: May 10, 2007

Date of Receipt: May 11, 2007

Our Reference Numbers: NDA 21-986/S-001, NDA 21-986/S-002

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, your application was filed on July 20, 2007, in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the requirement for pediatric studies for this application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please call me at (301) 796-1994.

Sincerely,

{See appended electronic signature page}

Sharon Thomas, BS, RHIT, CCRP
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Sharon Thomas

7/25/2007 04:07:13 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-986/S-001

Bristol-Myers Squibb Company
5 Research Parkway
P.O. Box 5100, Mailstop 3SIG-3021
Wallingford, CT 06492

Attention: Meenal Pai, Pharm.D.
Manager, Global Regulatory Sciences

Dear Ms. Pai:

Please refer to your May 10, 2007 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SPRYCEL® (dasatinib, BMS-354825) tablets 100 mg, received May 11, 2007.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on July 10, 2007 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Pharmacokinetic results, population PK report and pharmacokinetic data from studies CA180034 and CA180017 were not submitted.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Sharon Thomas, Regulatory Project Manager, at (301) 796-1994.

Sincerely,
{See appended electronic signature page}

Robert Justice, M.D.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Ramzi Dagher

7/24/2007 04:55:40 PM

Thomas, Sharon

From: Thomas, Sharon
Sent: Monday, June 25, 2007 4:37 PM
To: 'meenal.pai@bms.com'
Subject: sNDA 21-986; SPRYCEL (dasatinib, BMS-354825)

Dear Meenal,

The Division would like a presentation on your sNDA submitted May 10, 2007 for SPRYCEL (dasatanib) which provides for a new dosing regimen.

We have a tentative dates of Aug. 3, 2007 or Aug., 8, 2007 at 3:00 pm- 4:00 pm est.

Please confirm as soon as possible.

Thank you,

Sharon

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/s/

Sharon Thomas
6/25/2007 04:57:18 PM
CSO