Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product: SPRYCEL		
Name of Active Ingredient: Dasatinib		

SYNOPSIS

Final Clinical Study Report for CA180005

TITLE OF STUDY: A Phase 2 Study of Dasatinib (BMS-354825) in Subjects with Accelerated Phase Chronic Myeloid Leukemia Resistant to or Intolerant of Imatinib Mesylate

INVESTIGATORS/STUDY CENTERS: There were 79 investigators at 55 centers worldwide. Subjects were treated at 55 of these centers.

PUBLICATIONS: There were no peer-reviewed articles published on CA180005 at the time of this report.

STUDY PERIOD:

Study Initiation Date:	6-Dec-2004
Last Patient First Visit:	3-Aug-2005
Clinical Phase:	2
Study Completion Date:	3-Aug-2007

INTRODUCTION: This report summarizes the safety and efficacy results as of 03-Aug-2007 on all 174 subjects with 2 years of follow-up.

OBJECTIVES: The primary objective of this study was to estimate the major hematologic response (MaHR) rate and overall hematologic response (OHR) rate to dasatinib in subjects with accelerated phase chronic myeloid leukemia (CML) with primary or acquired resistance to imatinib.

METHODOLOGY: Eligible subjects received oral dasatinib at a starting dose of 70 mg twice daily (BID). Dose modifications were allowed for the management of disease progression or toxicity. Treatment continued until progression of disease or development of intolerable toxicity. All subjects were followed for a minimum of 30 days after the last dose of study therapy or until recovery from all toxic effects, whichever was longer. Follow-up visits occurred at least every 4 weeks until all study-related toxicities returned to baseline levels or ≤ Grade 1 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]), stabilized, or were deemed irreversible.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Subjects ≥ 18 years of age with accelerated phase CML resistant or intolerant to imatinib.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Dasatinib 70 mg BID continuous dosing; dose modifications were allowed for management of disease progression or toxicity; treatment continued until disease progression, or development of intolerable toxicity.

Dasatinib Batch Numbers

Strength	Batch Number
20 mg	4L77202, 4M64169, 5A04130/4M4311Z, 5A04132/4M4312Z, 5A04134/4M4313Z, 5C06213/5C4301Z, 5C06214/5C4302Z, 5E01515/5D4305Z, 5E01517, 5E01519/5D4333Z, 5E01522, 5E01523, 5E01524/5C4330Z, 5E01527/5D4306Z, 5E01529/5C4329Z, 5E01532, 5E01533, 5E01536, 5E01541, 5E01546, 6B19311/5J4323ZA
50 mg	4L77205, 4L85341, 5A10548, 5A10549/5A4307Z, 5A10557/5A4308Z, 5C05064/5B4305Z, 5C05065/5B4307Z, 5C08599/5B4306Z, 5C08601/5B4308Z, 5C08609/5B4310Z, 5H01126/5G4301Z, 5H01127/5G4302Z, 5K09694/5J4324Z, 5K09695/5J4325Z

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Not applicable.

CRITERIA FOR EVALUATION:

Efficacy: Co-primary endpoints were the rates of MaHR and OHR. Key secondary objectives included durability and time to hematologic response and cytogenetic responses. The hematologic responses were evaluated with regular blood draws and the cytogenetic responses were evaluated with regular bone marrow biopsies.

Safety: Assessment of safety was based on medical review of adverse events (AEs), clinical laboratory tests, and electrocardiograms (ECGs).

STATISTICAL METHODS: Summary statistics (mean, median, range for continuous variables and frequency for categorical variables) were provided for all pre-treatment characteristics including disease history and prior therapy. Efficacy responses were programmatically determined from hematologic laboratory values, bone marrow cytology and cytogenetics, and extramedullary disease. Response rates and 95% confidence intervals (CIs) were estimated. Kaplan-Meier estimates and 95% CIs were provided for the time to response (major and overall), duration of response, progression-free survival, and overall survival. Safety analyses included the frequency of assessment of adverse events, serious adverse events, deaths, discontinuations, and laboratory abnormalities. All analyses were presented for all treated subjects, imatinib-resistant and imatinib-intolerant subjects.

SUMMARY OF RESULTS:

Disposition, Demographics, and Other Pertinent Baseline Characteristics:

A total of 197 subjects were enrolled from 6-Dec-2004 to 3-Aug-2005 and 174 (13 imatinib-intolerant and 161 imatinib-resistant) received at least 1 dose of dasatinib. Twenty-three enrolled subjects never received treatment in CA180005. Of these 23, 13 subjects were switched to another dasatinib protocol.

As of the data cutoff, 45 (26%) subjects were still on study and 129 (74%) subjects discontinued dasatinib. Of these discontinuations, 55 (32%) were due to disease progression, 21 (12%) due to study drug toxicity, 13 (8%) due to subject request, 12 (7%) due to death, 4 (2%) due to an AE unrelated to study drug, 2 (1%) due to deterioration without progression, 1 (< 1%) due to lost to follow-up, and 1 (< 1%) due to non-compliance. Nineteen (11%) subjects discontinued due to 'other'. Reasons for study drug toxicity included pleural effusion (5 subjects), thrombocytopenia (3 subjects), myelosuppression (2 subjects), pancytopenia (2 subjects), gastrointestinal bleeding (2 subjects), bleeding from nose, ulcer, hemorrhage, dyspnea, neck pain, oral cavity mucositis, drug pneumonitis, suspected pulmonary toxicity, tachycardia, and pulmonary fibrosis (1 subject each, respectively).

Subjects ranged from 22 to 86 years of age. The subjects treated in this study were predominantly male (55%) and white (79%). Most patients had good performance status at study entry as defined by the ECOG.

All subjects had received prior imatinib therapy, consistent with entry criteria: 31% had received imatinib for 1 to 3 years and 52% had received an imatinib dosage > 600 mg/day.

All subjects had a long history of CML and were extensively pretreated. The median time from initial CML diagnosis to the start of dosing was 82 months for all treated subjects.

The median duration of therapy was 13.47 months (range 0.13 - 29.44 months) with 89 (51%) subjects on therapy for > 12 months. The median of the average daily dose of dasatinib was 107 mg.

Efficacy Results: Treatment with dasatinib 70 mg BID resulted in clinically important hematologic and cytogenetic response rates (Table 1). Duration of response was assessed in 112 subjects who achieved MaHR. Of these 112 subjects, 39 had progressed or died. The longest duration of response to date was 28.6+ months and the shortest duration of response was 0.9 months.

Table 1: Overall Summary of Efficacy - All Treated Subjects

	Number of Subjects (%)		
	Imatinib- intolerant N = 13	**Imatinib-resistant N = 161**	**Total N = 174**
Major Hematologic Response	9 (69.2%)	103 (64.0%)	112 (64.4%)
95% CI	38.6% - 90.9%	56.0% - 71.4%	56.8% - 71.5%
Overall Hematologic Response	12 (92.3%)	127 (78.9%)	139 (79.9%)
95% CI	64.0% - 99.8%	71.8% - 84.9%	73.2% - 85.6%
Major Cytogenetic Response	5 (38.5%)	65 (40.4%)	70 (40.2%)
95% CI	13.9% - 68.4%	32.7% - 48.4%	32.9% - 47.9%

Safety Results: Dasatinib demonstrated an acceptable safety profile in subjects with accelerated phase CML. Fluid retention-related AEs were reported in 114 (66%) subjects (Table 2). Of these 114, drug-related AEs were reported for pleural effusion (58 subjects), pericardial effusion (13 subjects), pulmonary edema (5 subjects), ascites (3 subjects), and pulmonary hypertension (1 subject).

A total of 41 (24%) subjects died. Thirteen (8%) of these 41 deaths were due to disease of which 12 were related to disease progression. The majority of treated subjects (173 [99%]) reported at least 1 AE. The most common Grade 3 to 5 AEs (excluding fluid-related events) were diarrhea (12%), pneumonia (10%), and dyspnea (10%). Drug-related AE was reported in 168 (97%) subjects. The most common Grade 3 to 5 drug-related AEs (≥ 5% and excluding fluid-related events) were diarrhea (8%), gastrointestinal hemorrhage (6%), dyspnea (5%), fatigue (5%), and pyrexia (5%). Overall, some degree of myelosuppression was common, both at baseline and on treatment.

Two of the 13 imatinib-intolerant subjects were discontinued from the current trial for AEs. The AEs reported in these 2 subjects were different from the AEs responsible for intolerance to imatinib, suggesting a partial lack of cross-intolerance between the 2 agents in this population.

Table 2: On-study Fluid Retention-related AEs by Grade - All Treated Subjects

System Organ Class Preferred Term	Number (%) of Subjects (Total = 174)		
	Any Grade	Severe (3 - 4)	Grade 5
Fluid Retention	114 (66)	21 (12)	3 (2)
Superficial Edema	81 (47)	3 (2)	0
Pleural Effusion	64 (37)	11 (6)	2 (1)
Other Fluid Related	47 (27)	11 (6)	1 (1)
Generalized Edema	18 (10)	1 (1)	0
Pericardial Effusion	15 (9)	4 (2)	0
CHF/Cardiac Dysfunction	8 (5)	2 (1)	1 (1)
Pulmonary Edema	9 (5)	3 (2)	0
Ascites	5 (3)	1 (1)	0
Pulmonary Hypertension	6 (3)	2 (1)	0

CONCLUSIONS:

Efficacy:

- Therapy with dasatinib (70 mg BID) resulted in a clinically important MaHR of 64% and an OHR of 79% in subjects with heavily-pretreated accelerated phase CML whose disease is resistant to imatinib.
- Therapy with dasatinib resulted in a clinically meaningful MCyR of 40% and CCyR of 33% in subjects with heavily-pretreated accelerated CML whose disease is resistant to imatinib.
- Durable responses were reported in 64% subjects resistant to imatinib who achieved MaHR. Of these, 35% progressed or died.
- Subjects with accelerated phase CML who are intolerant of imatinib were able to tolerate dasatinib and hematologic responses were observed in 12 of 13 (92%) subjects.

Safety:

- Dasatinib demonstrated an acceptable safety profile in subjects with heavily-pretreated accelerated phase CML, even those with compromised bone marrow functions.
- Subjects with accelerated phase CML who were intolerant to imatinib tolerated dasatinib, suggesting a partial lack of cross intolerance between the 2 agents.

Overall:

- Based on the efficacy results in this study, dasatinib is an important therapeutic option for subjects with accelerated phase CML that is resistant to imatinib and for subjects with accelerated phase CML who are intolerant of imatinib.

DATE OF REPORT: 21-Feb-2008