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 CA180006

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

INVESTIGATORS/ STUDY CENTERS: Subjects were enrolled and treated by 47 investigators at 49 sites

PUBLICATIONS: There were no peer-reviewed articles published on CA180006 at the time of this report.

STUDY PERIOD:

Study Initiation Date:	30-Dec-2004
Last Patient First Visit:	7-Jul-2005
Clinical Phase:	2
Study Completion Date:	7-Jul-2007

INTRODUCTION: This report summarizes the safety and efficacy results as of 7-Jul-2007 on all 109 subjects with a minimum of 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 myeloid blast 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 myeloid blast phase CML with primary or acquired resistance to imatinib or intolerance to imatinib.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Dasatinib administered orally at a starting dose of 70 mg BID; treatment to continue

until progression of disease or development of intolerable toxicity that could not be managed by dose modification.

Dasatinib Batch Numbers

Strength	Batch Number
20 mg	4L77202, 4M64169/4L4304Z, 5A04130/4M4311Z, 5A04132/4M4312Z, 5A04134/4M4313Z, 5C06213/5C4301Z, 5C06214/5C4302Z, 5E01515/5D4305Z, 5E01517, 5E01519/5D4333Z, 5E01522, 5E01523, 5E01527/5D4306Z, 5E01529/5C4329Z,5E01532, 5E01541, 5E01546, 6B19311/5J4323ZA
50 mg	4L77205, 4L85341, 5A10548, 5A10549/5A4307Z, 5A10557/5A4308Z, 5C05064/5B4305Z, 5C05065/5B4307Z, 5C08599/5B4306Z, 5C08601/5B4308Z, 5C08609/5B4310Z, 5H01127/5G4302Z, 5H01128/5G4303Z, 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) and the duration of response. 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 124 subjects were enrolled from 30-Dec-2004 to 7-Jul-2005 and 109 received at least 1 dose of dasatinib. Of the 109 treated subjects, 10 were imatinib-intolerant and 99 were imatinib-resistant. Fifteen enrolled subjects never received treatment: 11 subjects did not make the study criteria for myeloid blast CML, 1 subject had a screening failure (prolonged QT interval), and 3 subjects died prior to entering treatment.

As of the data cutoff, 6 subjects were still on study and 103 subjects discontinued dasatinib. Of these discontinuations, 48 (44%) were due to disease progression, 13 (12%) due to study drug toxicity, 13 (12%) due to death, 3 (3%) due to an AE unrelated to study drug, 3 (3%) due to deterioration without progression, 3 (3%) due to subject request, 2 (2%) due to non-compliance, and 18 (17%) due to ‘other’.

Subjects ranged between 21 and 81 years of age and 18% were > 65 years. The subjects treated in this study were predominantly male (58%) and white (71%). 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: 39% had received imatinib for 1 to 3 years and 50% had received an imatinib dosage > 600 mg/day.

Subjects in this study had a long history of CML and were extensively pretreated. The median time from initial diagnosis of CML to the start of dosing was 48 months.

The median duration of therapy was 3.5 months (range 0.03 - 29.4 months) with 45 (41%) subjects on therapy for > 6 months. The median of the average daily dose of dasatinib was 136 mg.

Efficacy Results: Treatment with dasatinib 70 mg BID resulted in clinically important hematologic and cytogenetic response rates (Table 1). The median time for subjects to achieve MaHR was 2.1 months. Duration of response was assessed in 36 subjects who achieved MaHR. Of these 36 subjects, 16 had progressed or died. The median duration of response was 22.4 months. The longest duration of response was 27.3+ months and the shortest duration of response has been 1.6 months.

Table 1: Overall Summary of Efficacy - All Treated Subjects with Lymphoid Blast CML

	Number of Subjects (%)		
	Imatinib- intolerant N = 10	**Imatinib-resistant N = 99**	**Total N = 109**
Major Hematologic Response 95% CI	2 (20.0%) 2.5% - 55.6%	34 (34.3%) 25.1% - 44.6%	36 (33.0%) 24.3% - 42.7%
Overall Hematologic Response 95% CI	4 (40.0%) 12.2% - 73.8%	50 (50.5%) 40.3% - 60.7%	54 (49.5%) 39.8% - 59.3%
Major Cytogenetic Response 95% CI	2 (20.0%) 2.5% - 55.6%	35 (35.4%) 26.0% - 45.6%	37 (33.9%) 25.1% - 43.6%

Safety Results: Dasatinib demonstrated an acceptable safety profile in subjects with myeloid blast CML. Fluid retention-related AEs were reported in 76 (70%) subjects (Table 2). Of these 76, drug-related AEs were reported for pleural effusion (43 subjects), pericardial effusion (9 subjects), CHF (2 subjects), pulmonary edema (2 subjects), ascites (3 subjects), and pulmonary hypertension (3 subjects).

A total of 55 (51%) subjects died. Thirty-two (29%) of these 55 deaths were due to disease progression. All 109 subjects reported at least 1 on-study AE. The most common Grade 3 to 5 AEs were pyrexia (14%) and dyspnea (11%). Drug-related AE was reported in 100 (92%) subjects. The most commonly occurring drug-related AEs were diarrhea (40%), vomiting (22%), pyrexia (22%), dyspnea (22%), nausea (20%), fatigue (18%), rash (14%), anorexia (13%), asthenia (13%), cough (12%), gastrointestinal hemorrhage (10%), headache (10%), epitaxis (10%), and petechiae (10%). Overall, some degree of myelosuppression was common, both at baseline and on treatment.

Two of the 10 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 8.4A: On-study Fluid Retention-related AEs by Grade - All Treated Subjects

System Organ Class Preferred Term	Number (%) of Subjects (Total = 109)		
	Any Grade	Severe (3 - 4)	Grade 5
Fluid Retention	76 (70)	28 (26)	1 (<1)
Superficial Edema	55 (50)	2 (2)	0
Pleural Effusion	48 (44)	21 (19)	0
Other Fluid Related	33 (30)	13 (12)	1 (<1)
Generalized Edema	13 (12)	2 (2)	0
Pericardial Effusion	11 (10)	3 (3)	1 (<1)
CHF/Cardiac Dysfunction	6 (6)	5 (5)	0
Pulmonary Edema	6 (6)	0	0
Ascites	5 (5)	2 (2)	0
Pulmonary Hypertension	4 (4)	2 (2)	0

CONCLUSIONS:

Efficacy

- Therapy with dasatinib (70 mg BID) resulted in a clinically important MaHR rate of 34% and an OHR rate of 51% in subjects with heavily-pretreated myeloid-blast CML whose disease was resistant to imatinib.
- Therapy with dasatinib resulted in a clinically important cytogenetic response rate of 35% in subjects with heavily-pretreated myeloid-blast CML whose disease was resistant to imatinib.
- Durable responses were reported in 35 subjects resistant to imatinib who achieved MaHR. Of these, 16 subjects progressed or died.
- Subjects with myeloid blast phase CML who were intolerant of imatinib were able to tolerate dasatinib and despite limited numbers of subjects, hematologic responses were observed in 4 of 10 subjects.

Safety

- Dasatinib was tolerable in subjects with heavily-pretreated myeloid-blast CML, even those with compromised bone marrow functions.
- Most subjects with heavily pretreated myeloid blast CML who are intolerant of imatinib are able to tolerate dasatinib without discontinuing from the study for AEs or study drug toxicities, 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 myeloid-blast phase CML that was resistant to imatinib and for subjects with myeloid-blast phase CML who were intolerant of imatinib.

DATE OF REPORT: 21-Feb-2008