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 CA180015: Lymphoid Blast Phase CML

TITLE OF STUDY: A Phase 2 Study of BMS-354825 in Subjects with Lymphoid Blast Phase Chronic Myeloid Leukemia or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia Resistant to or Intolerant of Imatinib Mesylate

INVESTIGATORS/ STUDY CENTERS: Subjects were enrolled and treated by 28 investigators at 28 sites.

PUBLICATIONS: There were no peer-reviewed articles published on CA180015 at the time of this report.

STUDY PERIOD:

Study Initiation Date:	5-Jan-2005
Last Patient First Visit:	13-May-2005
Clinical Phase:	2
Study Completion Date:	13-May-2007

INTRODUCTION: This report summarizes the safety and efficacy results as of 13-May-2007 on all 48 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 lymphoid blast phase CML subjects or Ph+ ALL with primary or acquired resistance to imatinib. Updated results for Ph+ ALL are presented in a separate report.

METHODOLOGY: This was an open-label Phase 2 study of dasatinib in subjects with imatinib-resistant lymphoid blast CML**.** A separate group of subjects with lymphoid blast phase CML intolerant to imatinib was also enrolled. Eligible subjects received 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 ≤ National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Grade 1, stabilized, or were deemed irreversible.

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

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

to continue until progression of disease or development of intolerable toxicity. Batch numbers are shown below.

Dasatinib Batch Numbers

Strength	Batch Number
20 mg	4L77202, 5A04130/4M4311Z, 5A04132/4M4312Z, 5C06213/5C4301Z, 5C06214/5C4302Z, 5E01519/5D4333Z, 5E01523, 5E01524/5C4330Z, 5E01529/5C4329Z, 5E01533
50 mg	4L77205, 5A10549/5A4307Z, 5A10557/5A4308Z, 5C05064/5B4305Z, 5C05065/5B4307Z, 5C08599/5B4306Z, 5C08601/5B4308Z, 5C08609/5B4310Z, 5H01128/5G4303Z

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 pretreatment 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 of the median duration of MaHR, OHR, and MCyR were provided along with their 95% CIs. The Kaplan-Meier estimate of the time to responses, progression-free survival, and overall survival was also reported. Safety analyses included the frequency of assessment of AEs, serious adverse events (SAEs), deaths, discontinuations, and laboratory abnormalities. All analyses were presented for all treated subjects.

SUMMARY OF RESULTS:

Disposition, Demographics, and Other Pertinent Baseline Characteristics: Fifty subjects with lymphoid blast CML were enrolled from 5-Jan-2005 to 13-May-2005 and 48 received at least 1 dose of dasatinib. Of the 48 treated subjects, 6 were imatinib-intolerant and 42 were imatinib-resistant. Two enrolled subjects died prior to entering treatment.

All 48 subjects are off study treatment. Twenty-six (54%) subjects discontinued due to disease progression, 8 (17%) due to death, 3 (6%) due to deterioration without progression, 2 (4%) due to study drug toxicity, and 2 (4%) due to an AE unrelated to study drug. The 2 cases of study drug toxicity included persistent neutropenia and thrombocytopenia (1 subject) and pulmonary hypertension (1 subject). Seven (15%) subjects discontinued due to 'other', which included transplant (6 subjects) and withdrawal of consent (1 subject).

Subjects ranged between 17 and 73 years of age and 10% were > 65 years. There were approximately equal numbers of female and male subjects. Subjects were predominantly white (96%). 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: 25% had received imatinib for 1 to 3 years and 52% 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 28 months.

The median duration of treatment was 2.9 months (range 0.1 - 27.5 months) with 38 (79%) subjects on therapy for ≤ 6 months. The median of the average daily dose of dasatinib was 140 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 17 subjects who achieved MaHR. Of these 17 subjects, 12 had progressed or died. The longest duration of response was 26.2 months and the shortest duration of response was 1.4+ months.

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

	Number of Subjects (%)		
	Intolerant N = 6	**Resistant N = 42**	**Total N = 48**
Efficacy Endpoint			
Major Hematologic Response	2 (33.3)	15 (35.7)	17 (35.4)
95% CI	4.3% - 77.7%	21.6% - 52.0%	22.2% - 50.5%
Overall Hematologic Response	2 (33.3)	17 (40.5)	19 (39.6)
95% CI	4.3% - 77.7%	25.6% - 56.7%	25.8% - 54.7%
Major Cytogenetic Response	4 (66.7)	21 (50.0)	25 (52.1)
95% CI	22.3% - 95.7%	34.2% - 65.8%	37.2% - 66.7%

Safety Results:

Dasatinib demonstrated an acceptable safety profile in subjects with lymphoid blast CML. Fluid retention-related AEs were reported in 25 (52%) subjects (Table 2). Of these 25, drug-related AEs were reported for pleural effusion (7 subjects), pericardial effusion (2 subjects), pulmonary edema (1 subject), and pulmonary hypertension (1 subject).

A total of 28 (58%) subjects died. Thirteen of these 28 deaths were due to disease of which 10 were related to disease progression. All subjects reported at least 1 on-study AE. The most common Grade 3 to 5 AEs were fatigue (13%), blast crisis (13%), pleural effusion (12%), pyrexia (10%), and abdominal pain (10%). Drug-related AE was reported in 42 (88%) subjects. The most commonly occurring drug-related AEs were diarrhea (33%), fatigue (27%), nausea (25%), vomiting (23%), headache (19%), rash (17%), pyrexia (17%), dyspnea (15%), pleural effusion (15%), and peripheral edema (13%). Overall, some degree of myelosuppression was common, both at baseline and on treatment.

Only 2 of the 6 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 (N = 48)		
	Any Grade	Severe (3 - 4)	Grade 5
Fluid Retention	25 (52)	5 (10)	1 (2)
Superficial Edema	18 (38)	0	0
Pleural Effusion	11 (23)	5 (10)	1 (2)
Other Fluid Related	10 (21)	3 (6)	0
Pericardial Effusion	4 (8)	0	0
Generalized Edema	3 (6)	0	0
CHF/Cardiac Dysfunction	2 (4)	2 (4)	0
Pulmonary Edema	2 (4)	1 (2)	0
Ascites	2 (4)	1 (2)	0
Pulmonary Hypertension	1 (2)	1 (2)	0

CONCLUSIONS:

Efficacy

- Therapy with dasatinib 70 mg BID resulted in clinically important MaHR rates of 35% and in OHR rates of 40% in subjects with lymphoid blast CML
- Therapy with dasatinib 70 mg BID resulted in clinically important MCyR rates of 52%
- The responses to dasatinib were durable: As of the data cutoff, 12 of the 17 subjects with MaHR had progressed or died
- Most of the subjects with heavily-pretreated lymphoid blast CML who are intolerant of imatinib are able to tolerate dasatinib and achieve hematologic and cytogenetic responses.

Safety

- Dasatinib 70 mg BID demonstrated an acceptable safety profile in subjects with heavily-pretreated lymphoid blast CML, even those with compromised bone marrow functions.
- Most subjects with heavily pretreated lymphoid 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 heavily-pretreated lymphoid blast CML that is resistant to imatinib and for subjects with heavily-pretreated lymphoid blast CML who are intolerant of imatinib.

DATE OF REPORT: 21-Feb-2008