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 CA180013

TITLE OF STUDY: A Phase 2 Study to Determine the Activity of BMS-354825 in Subjects with Chronic Phase Philadelphia Chromosome Positive Chronic Myeloid Leukemia who have Disease that is Resistant to High Dose Imatinib Mesylate (Gleevec®) or who are Intolerant of Imatinib

INVESTIGATORS/STUDY CENTERS: There were 89 investigators at 90 centers worldwide. Subjects were treated at 75 of these centers.

PUBLICATIONS: None

STUDY PERIOD:

Study Initiation Date:	10-Feb-2005
Last Patient First Visit:	10-Aug-2005
Clinical Phase:	2
Study Completion Date:	10-Aug-2007

INTRODUCTION: This report summarizes the safety and efficacy results as of 10-Aug-2007 on all 387 subjects with a minimum of 2 years of follow-up.

OBJECTIVES: The primary objective of this study was to estimate the major cytogenetic response (MCyR) rate to dasatinib in subjects with chronic phase chronic myeloid leukemia (CML) who had disease that was resistant to imatinib.

METHODOLOGY: This was an open-label Phase 2 study of dasatinib in subjects with chronic phase CML resistant to imatinib (> 600 mg/day) or ≤ 600 mg/day with mutations of the BCR-ABL gene, or who were intolerant of imatinib at any dose. Following screening, eligible subjects received dasatinib 70 mg continuously twice daily (BID). Dose escalation to 90 mg BID was allowed for subjects who showed evidence of progression or lack of response. Up to 2 dose reductions were allowed for toxicity. Treatment continued until progression of disease or development of intolerable toxicity or subject's decision to withdraw. 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. Subsequent follow-up visits were to occur at least every 4 weeks until all study-related toxicities returned to baseline levels, resolved to ≤ CTC Grade 1, stabilized, or were deemed irreversible.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Subjects ≥ 18 years of age with chronic phase CML who were resistant to imatinib (> 600 mg/day, or ≤ 600/day mg with mutation of BCR-ABL gene associated with a high level of imatinib resistance) or intolerant to imatinib at any dose.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Dasatinib 20 mg tablet and 50 mg tablet administered orally at a starting dose of

70 mg BID; treatment was to continue until progression of disease or development of toxicity that could not be managed by dose modification or until other protocol-defined criteria for discontinuation of study therapy were met.

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, 5E01521/5D4313Z, 5E01522, 5E01523, 5E01524/5C4330Z, 5E01527/5D4306Z, 5E01529/5C4329Z, 5E01532, 5E01533, 5E01536, 5E01541, 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, 5H01128/5G4303Z, 5K09694/5J4324Z, 5K09695/5J4325Z

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

CRITERIA FOR EVALUATION:

Efficacy: The primary endpoint was MCyR to dasatinib in treated subjects with chronic phase CML who had resistance to imatinib. The hematologic responses were monitored and evaluated with regular blood drawings. The cytogenetic responses were monitored and evaluated with regular bone marrow biopsies. Hematologic and cytogenetic responses were evaluated for all treated subjects.

Safety: Assessment of safety was based on medical review of adverse events (AEs), clinical laboratory tests, and electrocardiograms (ECGs). On-study AEs were graded in severity by the investigators according to the NCI CTCAE, version 3.0 grading system. The investigator adverse event terms were coded and grouped by preferred term and system organ class using the MedDRA dictionary, version 10.0 and were summarized by any grade, Grade 3 to 4, and Grade 5.

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 extramedullary disease. Response rates (hematologic and cytogenetic) along with their 95% exact confidence intervals (CIs) were estimated. Kaplan-Meier estimates of the median duration of MCyR, CCyR, and complete hematologic response (CHR) 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, imatinib resistant and imatinib intolerant subjects.

SUMMARY OF RESULTS:

Disposition, Demographics, and other Pertinent Baseline Characteristics:

A total of 424 subjects were enrolled between 10-Feb-2005 and 10-Aug-2005, and 387 (99 imatinib-intolerant and 288 imatinib-resistant) received at least 1 dose of dasatinib. Thirty-seven enrolled subjects did not receive dasatinib in this study. A total of 229 (59%) subjects discontinued study drug. Of these discontinuations, a small number (47 subjects) were due to disease progression. Remaining discontinuations were due to study drug toxicity (75 subjects), death (6 subjects), subject request

(14 subjects), AE unrelated to study drug (8 subjects), non-compliance (5 subjects), deterioration without progression (1 subject), lost to follow-up (2 subjects), and 'other' (71 subjects). Of these 71 subjects, 49 discontinued due to study closure/completion with the majority on-study for ≥ 2 years. As of the data cutoff, 156 (40%) subjects were still receiving treatment in the study and 231 (60%) subjects discontinued dasatinib.

The majority of subjects (89%) were white, the median age was 58 years (range 21 - 85) with similar numbers of males (49%) and females (51%). The ECOG performance status of the majority of subjects (71%) was 0.

All patients had received prior imatinib treatment consistent with entry criteria. The median time from initial CML diagnosis to first dose of dasatinib was 61 months (range 2.8 - 251 months). A majority of imatinib-resistant subjects (67%) had received more than 3 years of prior therapy with imatinib; the highest dose of imatinib was > 600 mg/day in 72% of subjects. The majority of imatinib-resistant subjects (84%) had achieved a CHR as their best response on imatinib; fewer subjects (100 of 288; 35%) had shown MCyR (complete or partial) as their best cytogenetic response with imatinib therapy.

A majority of imatinib-intolerant subjects (58%) had received less than 1 year of prior therapy with imatinib; the highest dose of imatinib was 400-600 mg/day in 92% of subjects. The majority of imatinib-intolerant subjects (77%) had achieved a CHR as their best response on imatinib; fewer subjects (43 of 99; 44%) had shown MCyR (complete or partial) as their best cytogenetic response with imatinib therapy.

Efficacy Results:

The efficacy of dasatinib was demonstrated consistently across all efficacy endpoints in the primary target population of imatinib-resistant subjects as well as in imatinib-intolerant subjects (Table 1).

Table 1: Summary of Efficacy Results - All Treated Subjects

	Number of Subjects (%)		
Imatinib Status	Intolerant N=99	Resistant N=288	Total N=387
Complete Hematologic Response	93 (93.9%)	259 (89.9%)	352 (91.0%)
95% exact CI	87.3% - 97.7%	85.9% - 93.2%	87.6% - 93.6%
Major Cytogenetic Response	81 (81.8%)	159 (55.2%)	240 (62.0%)
95% exact CI	72.8% - 88.9%	49.3% - 61.0%	57.0% - 66.9%

Most subjects who achieved CHR did so within the first 2 months of treatment and nearly half of the subjects who achieved MCyR did so within the first 6 months with most subjects achieving MCyR by 1 year. Responses were durable with no evidence of a plateau. Only 5 (5%) imatinib-intolerant subjects and 47 (18%) imatinib-resistant subjects who achieved a CHR died or progressed. Two (2%) imatinib-intolerant subjects and 19 (12%) imatinib-resistant subjects with MCyR progressed.

The median duration of therapy was 24.15 months (range 0.03 - 30.62 months) with 279 (72%) subjects on therapy for > 12 months. The median of the average daily dose of dasatinib was 97 mg.

Safety Results:

Dasatinib demonstrated an acceptable safety profile in subjects with chronic phase CML. Myelosuppression and fluid retention-related events were the most common toxicities. Approximately 45% of subjects with normal platelet and normal neutrophil counts at baseline experienced Grade 3 to 4 thrombocytopenia and neutropenia. Fluid retention-related AEs were reported in 235 (61%) subjects (Table 2). Of these 235, drug-related AEs were reported for pleural effusion (137 subjects), pericardial effusion (20 subjects), CHF (16 subjects), pulmonary edema (7 subjects), pulmonary hypertension (7 subjects), and ascites (1 subject).

A total of 19 (5%) subjects died (all imatinib-resistant) of which 7 were related to disease progression. The majority of treated subjects (99.7%) reported at least 1 AE, regardless of relationship to study drug. The most common Grade 3 to 5 AE (occurring ≥ 5% excluding fluid-related events) was dyspnea (8%). Drug-related on-study AEs (≥ 10% cutoff) regardless of grade were reported in 378 (98%) of all treated subjects. The most common Grade 3 to 5 drug-related non-hematologic AE was dyspnea (6%).

Of these 99 subjects, only 3 had the same Grade 3-4 toxicity with dasatinib as they did with imatinib, and all 3 subjects were able to continue treatment after dose reduction.

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

System Organ Class Preferred Term	Number (%) of Subjects (Total = 387)		
	Any Grade	Severe (3 - 4)	Grade 5
Fluid Retention	235 (61)	60 (16)	0
Superficial Edema	150 (39)	1 (< 1)	0
Pleural Effusion	142 (37)	37 (10)	0
Other Fluid Related	74 (19)	28 (7)	0
Generalized Edema	25 (6)	3 (1)	0
Pericardial Effusion	21 (5)	4 (1)	0
CHF/Cardiac Dysfunction	28 (7)	18 (5)	0
Pulmonary Edema	10 (3)	3 (1)	0
Ascites	2 (1)	0	0
Pulmonary Hypertension	11 (3)	3 (1)	0

CONCLUSIONS:

Efficacy

- With durations of dasatinib exposure up to 30 months, response rates continue to improve
- Therapy with dasatinib (70 mg BID) results in a clinically relevant MCyR rate of 55% in pretreated subjects with chronic phase CML whose disease is resistant to imatinib
- A clinically relevant CHR rate of 90% is also achieved in this population
- Subjects with chronic phase CML who are intolerant of imatinib are able to tolerate dasatinib resulting in a 94% CHR rate and a 82% MCyR rate
- Durable cytogenetic responses were reported in 159 subjects resistant to imatinib who achieved MCyR. Of these, 19 subjects progressed

Safety

- Dasatinib is safe and tolerable in subjects with heavily pretreated chronic phase CML. Thrombocytopenia, fluid retention, and pleural effusion were among the most relevant AEs
- The majority of subjects with chronic phase CML who are intolerant of imatinib are able to receive dasatinib without experiencing the same adverse events that caused them to discontinue imatinib therapy

Overall

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

DATE OF REPORT: 21-Feb-2008