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

Clinical Study Report for CA180035

TITLE OF STUDY: A Randomized, Two-arm, Multicenter, Open-label Phase III Study of BMS-354825 Administered Orally at a Dose of 70 mg Twice Daily or 140 mg Once Daily in Subjects with Chronic Myeloid Leukemia in Accelerated Phase or in Myeloid or Lymphoid Blast Phase or with Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia who are Resistant or Intolerant to Imatinib Mesylate

INVESTIGATORS/STUDY CENTERS: 129 principal investigators/638 subjects were enrolled at 130 sites (129 unique sites - sites 136 and 137 in South Africa are the same): 65 in Europe (includes Russia), 35 in North America (US and Canada), 9 in South America, 10 in Asia, 6 in Australia, and 5 in South Africa.

PUBLICATIONS:
Kantarjian HM, Ottmann O, Pasquini R, Goh YT, Kim DW, Van Tornout J, et al. Dasatinib (SPRYCEL) 140 mg once daily (QD) vs 70 mg twice daily (BID) in patients (pts) with advanced phase chronic myeloid leukemia (ABP-CML) or Ph(+) ALL who are resistant or intolerant to imatinib (im): results of the CA180035 study. Blood 2006;108:224a (Abstract 746).

STUDY PERIOD: Study Initiation Date: 3-Jun-2005 **CLINICAL PHASE:** 3

Study Completion Date: 24-Mar-2008 (LPLV).

OBJECTIVES: The primary objective of this study was to compare the efficacy of dasatinib when administered to subjects at 140 mg once daily (QD) relative to dasatinib administered at 70 mg twice daily (BID) in overall population.

The main secondary objective was to estimate the difference in major hematologic response (MaHR) rates between treatment groups (QD vs BID) by disease phase and imatinib status. Other secondary objectives were: 1) to estimate the rates of MaHR, overall hematologic response (OHR), and major cytogenetic response (MCyR) by treatment group, disease phase, and imatinib status; 2) to assess time to and duration of MaHR by treatment group, disease phase, and imatinib status; 3) to assess progression-free and overall survival by treatment group, disease phase, and imatinib status; 4) to assess the safety of dasatinib, in particular the incidence of adverse events (AEs), the number of dose reductions, interruptions, and treatment discontinuations for toxicity by treatment group; 5) to collect population pharmacokinetic (PK) data; 6) to describe the spectrum of mutations at baseline and at time of progressive disease; 7) to explore the roles of BCR-ABL mRNA expression and point mutations in the BCR-ABL gene as predictors or surrogates of responses.

METHODOLOGY: This was a randomized 2-arm multicenter, open-label Phase 3 study of dasatinib for subjects with accelerated phase CML, blast phase CML, or Ph+ ALL, either resistant or intolerant to imatinib. Subjects were stratified by disease status (accelerated phase CML, myeloid blast phase CML, and

lymphoid blast phase CML, or Ph+ ALL) and imatinib status (resistant or intolerant). Subjects were randomized within each strata to receive dasatinib at a dose of 70 mg BID or 140 mg QD. 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. Subsequent follow-up visits were to occur at least every 4 weeks until all study-related toxicities returned to baseline levels (or ≤ Grade 1), stabilized, or were deemed irreversible. Follow-up observations for survival analysis were done every 3 months until subject's death or lost to follow-up.

NUMBER OF SUBJECTS (Planned and Analyzed): A total of 638 subjects were enrolled, 611 were randomized (478 imatinib-resistant and 133 imatinib-intolerant subjects), and 609 received at least 1 dose of dasatinib. Data cutoff date was 05-May-2008.

Number of Treated Subjects by Disease Type and Schedule							
Accelerated N = 316		Myeloid Blast N = 148		Lymphoid Blast N = 61		Ph+ ALL N = 84	
QD N = 157	BID N = 159	QD N = 74	BID N = 74	QD N = 33	BID N = 28	QD N = 40	BID N = 44

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Subjects ≥ 18 years of age with accelerated phase CML, myeloid blast phase CML, lymphoid blast phase CML, or Ph+ ALL and a primary or acquired hematologic resistance to imatinib or intolerance to imatinib were included.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Dasatinib was administered orally at a starting dose of 140 mg QD or 70 mg BID; treatment was to continue until progression of disease or development of intolerable toxicity or subject's decision to withdraw. Batch numbers were: 20 mg tablets - 4L77202; 5A04130/4M4311Z; 5A04132/4M4312Z; 5A04134/4M4313Z; 5C06213/5C4301Z; 5C06214/5C4302Z; 5E01515/5D4305Z; 5E01517; 5E01519/5D4333Z; 5E01522; 5E01523; 5E01524/5C4330Z; 5E01527/5D4306Z; 5E01529/5C4329Z; 5E01533. 50 mg tablets - 4L77205; 5A10548; 5A10549/5A4307Z; 5A10557/5A4308Z; 5C05064/5B4305Z; 5C05065/5B4307Z; 5C08599/5B4306Z; 5C08601/5B4308Z; 5C08609/5B4310Z; 5H01128/5G4303Z; 4M67208; 4L77205; 5A10548.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Gleevec 400 mg tablets - Batch number was 4M67208.

CRITERIA FOR EVALUATION:

Efficacy: The primary objective was a comparison of efficacy (non-inferiority) between the QD and BID schedules. The primary efficacy endpoint was the rate of MaHR. Secondary endpoints included rates of OHR and MCyR, the difference of MaHR between QD and BID groups, time to and duration of MaHR, progression-free survival and overall survival.**Safety:** Toxic effects were assessed continuously. Assessment of safety was based on medical review of AEs, clinical laboratory tests, and electrocardiograms (ECGs). On-study AEs were graded by severity according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. The investigator AE terms were coded and grouped by preferred term and system organ class using the MedDRA dictionary, version 9.0 and were summarized by any grade, Grade 3 to 4, and Grade 5.

STATISTICAL CONSIDERATIONS:

Demographic and baseline characteristics were tabulated by group (QD vs BID), disease phase, and imatinib status using descriptive statistics. The primary objective of this study was to compare the efficacy

of dasatinib when administered to subjects at 140 mg QD relative to dasatinib administered at 70 mg BID in the overall population. The QD schedule was considered similar (non-inferior) to the BID schedule if the lower bound of the 2-sided 95% asymptotic confidence interval of the difference in major hematologic response rates (MaHRR QD minus MaHRR BID) was ≥ -12%. The main secondary objective was to estimate the difference in MaHR between QD and BID groups by disease phase and imatinib status. Two-sided exact 95% confidence intervals of the differences were provided based on the method proposed by Agresti and Min.

Response rates (MaHR, OHR, and MCyR) were provided by group, disease phase, and imatinib status. Two-sided exact 95% CIs were provided based on the method proposed by Clopper and Pearson. The distribution of the progression-free and overall survival and time to and duration of MaHR and MCyR were estimated using the Kaplan-Meier product limit method. The median of the distribution was provided along with its 95% CI.

All analyses of efficacy were performed using the dosing schedule as randomized. Two sensitivity analyses were performed for the primary objective. The first sensitivity analysis used the method of DerSimonian and Laird, assuming a fixed effects model, which adjusts the estimate of rate of MaHR differences for the stratification factors (imatinib status and disease type) as randomized. Adjusted estimates of rate of MaHR differences and associated 2-sided 95% CI were computed. The second sensitivity analysis was a per-protocol analysis, which provides estimates of the rate of MaHR difference and associated 95% CI for subject's who did not have a significant protocol deviation with the exception of the subjects whose only significant protocol deviation was switch in assigned treatment group (N=5). As a secondary analysis, MaHR and OHR rates and difference between groups of MaHR and OHR rates, were estimated based on the dataset of randomized subjects.

Safety analyses included the frequency of assessment of AEs, serious adverse events (SAEs), deaths, AEs leading to discontinuation, and laboratory abnormalities. Toxicity rates, using the worst CTC Grade per subject, for selected ≥ Grade 3 drug-related AEs (eg, fluid retention, pleural/pericardial effusion, myelosuppression, and dose reduction due to toxicity) were compared between the 2 groups using the Fisher exact test. All analyses were presented for all treated subjects.

SUMMARY OF RESULTS:

Disposition, Demographics, and Other Pertinent Baseline Characteristics:

Of the 638 enrolled subjects, 611 were randomized and 609 received at least 1 dose of dasatinib. Of the 609 treated subjects, 128 subjects remain on study as of 05-May-2008 and 481 discontinued study treatment (243 subjects in the QD group and 238 subjects in the BID group).

The age of the study population ranged from 15 to 84 years with an overall mean age of 52.3 years and a median age of 55.0 years. The 2 groups were balanced for age, gender, and race. Subjects in the 2 groups had the same length of initial CML (58 months median time for both). Subjects were extensively pretreated in both treatment groups.

All randomized subjects in this study had received prior imatinib treatment and were either resistant (N=477) or intolerant (N=132) to imatinib. The majority of imatinib-resistant subjects in the QD and BID groups had acquired resistance (63% and 62%, respectively). A similar number of subjects in the QD group vs the BID group had primary resistance to imatinib (14% and 16%, respectively). The intolerant subjects were equally distributed at baseline between the QD and BID groups (22% and 21%, respectively). A small difference was reported among the 2 groups in hematologic response to imatinib therapy; more subjects in the QD group vs the BID group reported a CCyR (24% vs 22%) and minimal cytogenetic response (11% vs 6%) to imatinib therapy.

Efficacy Results: Efficacy results pooled over all the disease phases demonstrated the non-inferiority of the QD schedule of treatment to the BID schedule. In randomized subjects, hematologic responses were similar between the 2 groups with a MaHR of 51% in the QD group and 50% in the BID group. The difference in

MaHR rate between the QD and BID groups was 0.8% (95% CI: -7.1% - 8.7%). The non-inferiority of the QD schedule to the BID schedule was also supported by two specified sensitivity analyses. In the analysis adjusted by stratification factors, the difference in MaHR rate was 0.7% (95% CI: -6.5% - 8.0%) and in the per-protocol analysis, the difference in MaHR rate was 2.1% (95% CI: -6.1% - 10.2%).

The median time to MaHR was 1.9 months in both groups. Among subjects who achieved a MaHR, the median duration of response was similar in the QD group vs the BID group (21.2 months vs 24.7 months, respectively). Overall, of the 155 subjects with MaHR in the QD group, 73 progressed. In the BID group, 60 of the 152 subjects with MaHR progressed. When evaluated within each disease phase, the number of subjects who progressed was similar between the QD and BID groups in subjects.

Efficacy results pooled over all the disease phases as well as individual disease phase showed little difference between the QD and BID groups in MCyR (42% vs 41%, respectively) with a difference in rate of -0.2% (95% CI: -7.6% - 8.0%). The time to MCyR was 1.9 months in both groups.

Among subjects who achieved a MCyR, the median duration of response was shorter in the QD group vs the BID group (13.1 months vs 22.2 months, respectively). Of the 127 subjects with MCyR in the QD group, 65 progressed. In the BID group, 53 of the 126 subjects with MCyR progressed.

Progression-free survival (PFS) was similar between the 2 treatment groups. The median length of PFS was 7.6 months in the QD group vs 10.4 months in the BID group with a QD/BID hazard ratio of 1.07 (95% CI: 0.88 - 1.32). Assessment of PFS by disease phase showed little difference between the QD and BID groups.

Safety Results:

Of the 609 treated subjects, 321 subjects died. Of the 321 deaths, 126 subjects died within 30 days of last dose of study therapy. The number of deaths reported within 30 days of treatment was similar between the QD and BID groups (QD: 65 subjects and BID: 61 subjects). Nearly half of these deaths were due to disease progression in both the groups (QD: 35 subjects and BID: 25 subjects). A clear difference between the two groups was observed in deaths within 30 days of last dose of study therapy due to cardiovascular disease and infection; 2 subjects in QD group compared to 7 subjects in the BID group died from cardiovascular disease, 11 subjects in the QD group compared to 18 subjects in the BID group died from infection. Death from fatal bleeding was similar between the QD and BID groups with 8 subjects and 6 subjects, respectively.

Adverse events that led to discontinuation of study therapy were similar in the QD group (N=97; 32%) and the BID group (N=95; 31%). Drug-related AEs that led to discontinuation of study therapy were similar in the QD group (N=41; 14%) and the BID group (N=50; 16%). A difference was however noted among the 2 groups in drug-related pleural effusion events that led to discontinuation of study therapy; 6 (2%) subjects in the QD group and 14 (5%) subjects in the BID group.

Specific analyses were performed on fluid retention events as AEs of special interest. Table 1 summaries these AEs by group in all treated subjects pooled across disease phase. Pleural effusion was reported in fewer subjects in the QD group compared with the BID group (24% vs 36%) (p=0.001). In both groups, the majority of pleural effusions were drug-related. The number of subjects with drug-related other fluid-related events (including generalized edema, pulmonary edema, CHF/cardiac dysfunction, and pericardial effusion) was lower in the QD group (5%) compared to BID group (13%).

Table 1: Adverse Events of Special Interest by Relationship Pooled Across Disease Phase; Treated Subjects				
	Number (%) of Subjects			
	QD N = 304		BID N = 305	
	Any Relationship	Related	Any Relationship	Related
Fluid Retention	128 (42)	97 (32)	153 (50)	130 (43)
Pleural Effusion	72 (24)	60 (20)	109 (36)	99 (33)
Superficial Edema	77 (25)	46 (15)	79 (26)	57 (19)
Other Fluid Related	25 (8)	15 (5)	59 (19)	41 (13)
CHF/Cardiac Dysfunction	8 (3)	3 (1)	12 (4)	6 (2)
Pulmonary Edema	7 (2)	4 (1)	13 (4)	8 (3)
Pericardial Effusion	6 (2)	5 (2)	22 (7)	17 (6)
Generalized Edema	7 (2)	5 (2)	16 (5)	10 (3)
Pulmonary Hypertension	1 (< 1)	0	5 (2)	4 (1)
Ascites	1 (< 1)	0	4 (1)	3 (1)

CONCLUSIONS:

Efficacy

- Dasatinib was efficacious in both schedules with the QD group displaying non-inferior MaHR rates compared with the BID group. Consistent with the results observed in the overall population, when analyzed by each disease phase (accelerated, myeloid and lymphoid blast phase and Ph+ ALL), the MaHR rates were similar in the two treatment groups
- MaHR and MCyR were durable; median durations were similar in the QD group and the BID group, both in the overall population as well as in individual disease phases

Safety

- Both dose schedules were tolerable in subjects in the overall population. This result was consistently observed in individual disease phases as well
- The QD schedule was associated with fewer dose reductions and interruptions vs the BID schedule
- Fewer subjects in the QD group than in the BID group reported fluid retention-related AEs of all grades, including pleural effusion, pulmonary edema, pericardial effusion, and CHF

Overall

- The 140 mg QD schedule represents the optimal risk/benefit ratio and is the recommended dose in advanced phase CML (accelerated, myeloid and lymphoid blast phase) and Ph+ ALL subjects

DATE OF REPORT: 18-Jul-2008