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

TITLE OF STUDY: A Randomized Multicenter Open Label Study of BMS-354825 vs Imatinib Mesylate (Gleevec®, Glivec®) 800 mg/day in Subjects with Chronic Phase Philadelphia Chromosome-positive Chronic Myeloid Leukemia Who Have Disease That Is Resistant to Imatinib at a Dose of 400 - 600 mg/day

INVESTIGATORS/ STUDY CENTERS: A total of 107 sites worldwide participated in this study; 53 of the 107 sites treated at least 1 subject.

PUBLICATIONS: None

CLINICAL PHASE: 2

STUDY PERIOD: Study Initiation Date: 10-Feb-2005
Study Completion Date: 20-Nov-2007

OBJECTIVES: The primary objective was to estimate the rate of major cytogenetic response (MCyR) of dasatinib 70 mg BID and imatinib 800 mg/day (400 mg BID) at 12 weeks in subjects with chronic phase (CP)-chronic myeloid leukemia (CML) resistant to imatinib 400 to 600 mg/day. Key secondary objectives included cytogenetic response (MCyR and complete cytogenetic response [CCyR]) and hematologic response at any time prior to crossover.

METHODOLOGY: This was an open-label, randomized, Phase 2 study of dasatinib and imatinib in subjects with chronic phase CML who were resistant to imatinib 400 to 600 mg/day. Eligible subjects were randomized in a 2-to-1 ratio to either dasatinib 70 mg BID or imatinib 400 mg BID, with continuous daily treatment. Randomization was stratified by site and cytogenetic response on prior imatinib therapy (any prior response). Dasatinib dose modifications were allowed in case of disease progression or lack of response or to manage drug toxicity. No dose escalation was allowed for imatinib. Dose reduction of imatinib to 600 mg/day was allowed, provided the subject had not previously been treated at that dose level. Subjects with lack of response, confirmed disease progression or persistent intolerance despite dose reduction could be crossed over to the alternative treatment after an adequate washout period (2 days for dasatinib, 1 week for imatinib). After crossover, treatment continued until further disease progression or development of intolerable toxicity. Cytogenetic assessment was performed every 12 weeks and at the time of crossover. Hematologic assessment was performed weekly up to 12 weeks and every 3 months thereafter. Database lock for this study was 20-Nov-2007.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Subjects were ≥ 18 years of age with CP-CML, resistant to imatinib 400 to 600 mg/day.

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

Study Medication	Batch Numbers		
Dasatinib 5 mg	5F02041		
Dasatinib 20 mg	4L77202	5C06214 / 5C4302Z	5E01524 / 5C4330Z
	4M64169	5E01515 / 5D4305Z	5E01527 / 5D4306Z
	5A04130 / 4M4311Z	5E01517	5E01529 / 5C4329Z
	5A04132 / 4M4312Z	5E01519 / 5D4333Z	5E01532
	5A04134 / 4M4313Z	5E01522	5E01533
	5C06213 / 5C4301Z	5E01523	5E01536
	5E01541	6B19311 / 5J4323ZA	
Dasatinib 50 mg	4L77205	5A10557 / 5A4308Z	5C08601 / 5B4308Z
	4L85341	5C05064 / 5B4305Z	5C08609 / 5B4310Z
	5A10548	5C05065 / 5B4307Z	5H01128 / 5G4303Z
	5A10549 / 5A4307Z	5C08599 / 5B4306Z	5H01126 / 5G4303Z
	5H01127 / 5G4302Z	5K09694 / 5J4324Z	5K09695 / 5J4325Z
	6C18621		

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: Imatinib was administered orally at a starting dose of 400 mg BID.

Study Medication	Batch Numbers		
Imatinib mesylate 100 mg	4M67207	5M04234	
	5C02672 / F0005	6F19568 / F0018	
Imatinib mesylate 400 mg	4M67208	6M66171 / F4070	5M04233
	5C02678 / F4073	5M04233 / F0010	7E24380 / F0038

CRITERIA FOR EVALUATION:

Efficacy: The primary efficacy endpoint was MCyR at 12 weeks. MCyR was defined as the rate of CCyR plus the rate of partial cytogenetic response (PCyR). Hematologic response and major molecular response (MMR) were secondary endpoints. Progression free survival (PFS) and time to treatment failure were also assessed.

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

STATISTICAL METHODS: Hematologic responses were programmatically determined from hematologic laboratory values, peripheral blood cytology, karyotype, and extramedullary disease. The cytogenetic response rate was determined based on karyotype. The MCyR rate at 12 weeks (primary efficacy endpoint) and difference between treatment groups, together with their 95% exact confidence intervals (CIs) and p-value for the difference were provided. The Clopper-Pearson method was used for the CI of the rates and the Agresti-Min method was used to for the CI of the difference and for the calculation

of the p-value. Similar analyses were conducted for the secondary endpoints: hematologic response and cytogenetic response at any time. Kaplan-Meier analyses of duration of MCyR and hematologic response, PFS, and time to treatment failure were performed. The major molecular response (MMR) rate was defined as the proportion of subjects who achieved a MMR at any time during the treatment period. MMR rates prior to crossover were provided for both treatment groups. In addition, the hazard ratio and corresponding p-value were provided for the PFS and time to treatment failure. Safety analyses included the frequency of AEs, serious adverse events (SAEs), and laboratory abnormalities.

SUMMARY OF RESULTS:

Disposition of Subjects, Demographics and Other Pertinent Baseline Characteristics, and Exposure:

150 subjects were randomized (101 to dasatinib and 49 to imatinib); all randomized subjects were treated. As of 20-Dec-2007, 51 (50%) dasatinib-treated subjects and 9 (18%) imatinib-treated subjects were still on initial treatment. Twenty (20%) dasatinib-treated subjects discontinued and crossed over to receive imatinib and 39 (80%) imatinib-treated subjects discontinued and crossed over to receive dasatinib.

As of 20-Dec-2007, 19 of 39 (49%) subjects who had crossed over to dasatinib and 8 of 20 (40%) subjects who had crossed over to imatinib were still receiving their second treatment. Twenty (20) of 39 (51%) dasatinib subjects and 12 of 20 (60%) imatinib subjects had discontinued their second treatment.

Fifty three percent (53%) of the subjects in the dasatinib group and 45% of the subjects in the imatinib group were male. The majority of subjects in each group were white and the median age of each group was 51 years (range 24-85 years). Most subjects had an ECOG performance status score of 0 (~ 70% in each group) or 1 (~ 26% in each group).

Treatment groups were balanced with respect to CML disease characteristics and prior therapy with the exception of imatinib-resistant mutations at baseline. Imatinib-resistant mutations were detected in 44% (41/93) of dasatinib-treated subjects and in 24% (11/46) of imatinib-treated subjects.

Treatment duration was longer in the dasatinib group (median: 22.5 months [range: 0.2 to 29.4 months]) than in the imatinib group (median: 3.1 months [range: 0.2 to 26.3 months]).

Efficacy:

Prior to Crossover: A complete hematologic response (CHR) and MCyR was achieved by a higher proportion of subjects in the dasatinib group than in the imatinib group. Response rates based on assessment of subjects with ≥ 20 metaphases was consistent with those achieved in all randomized subjects.

Response Rates Prior to Crossover- All Randomized Subjects

	Number of Subjects (%)	
Efficacy Endpoints	**Dasatinib N = 101**	**Imatinib N = 49**
Cytogenetic Response at 12 Weeks		
MCyR	36 (36)	14 (29)
Difference [95%CI, p value]	7% [-9.8, +22.2, p=0.4025]	
CCyR	22 (22)	4 (8)
Difference [95%CI, p value]	14% [+0.6, +24.8, p=0.0409]	
PCyR	14 (14)	10 (20)
Cytogenetic Response at Any Time Prior to Crossover		
MCyR	54 (53)	16 (33)
Difference [95%CI, p value]	21% [+3.6, +36.8, p=0.0169]	
CCyR	44 (44)	9 (18)

Response Rates Prior to Crossover- All Randomized Subjects		
PCyR	10 (10)	7 (14)
Hematologic Response at Any Time Prior to Crossover		
CHR	94 (93)	40 (82)
Difference [95%CI, p value]	11% [+0.7, +25.2, p=0.0341]	

Subpopulation Analyses: Subpopulation analyses of MCyR and CCyR rates at any time prior to crossover showed that dasatinib was an effective therapeutic option across a number of difficult to treat subgroups.

Duration of Response: Responses to dasatinib were durable in dasatinib-treated subjects with chronic phase CML. The duration of MCyR ranged from 2.8 to 25.0+ months for the dasatinib group and from 1.1 to 22.0+ months for the imatinib group. The duration of CHR ranged from 2.2 to 29.0+ months for the dasatinib group and 1.4 to 27.0+ months for the imatinib group.

Mutation Analysis: In subjects with imatinib-resistant mutations, response rates at any time prior to crossover were higher for the dasatinib group than for the imatinib group: CHR rate 88% vs 55% and MCyR rate 46% vs 27%, respectively.

Progression Free Survival: Of the 150 randomized subjects, 13 in the dasatinib group and 10 in the imatinib group had progressed as of 20-Nov-2007. The hazard ratio (dasatinib/imatinib) was 0.26 (95% CI 0.11, 0.62, $p < 0.0012$).

Time to Treatment Failure: Of the 150 treated subjects, 43 in the dasatinib group and 40 in the imatinib group had failed initial treatment as of 20-Nov-2007. The hazard ratio (dasatinib/imatinib) for time to treatment failure was 0.23 (95% CI 0.14, 0.35, $p < 0.0001$).

Major Molecular Response: The major molecular response rate at any time prior to crossover was 29% for the dasatinib group and 12% for the imatinib group.

After Crossover: Subjects treated with dasatinib after crossover achieved higher rates of CHR and MCyR than subjects treated with imatinib.

Response Rates After Crossover- Subjects Evaluable for After Crossover Response

	Number of Subjects (%)	
Efficacy Endpoints	**Dasatinib**	**Imatinib**
Hematologic Response	**N = 39**	**N = 20**
CHR	37 (95)	13 (65)
Cytogenetic Response		
MCyR	19 (49)	3 (15)
CCyR	15 (39)	0
PCyR	4 (10)	3 (15)

Safety Results:

Prior to Crossover

The table below summarizes clinically relevant AEs and laboratory test results prior to crossover.

Summary of Safety Prior to Crossover - All Treated Subjects

	Number of Subjects (%)	
	Dasatinib N = 101	**Imatinib N = 49**
Any AE	100 (99)	45 (92)
Grade 3-4 AEs	67 (66)	21 (43)
Drug-related AEs	94 (93)	44 (90)
Drug-related Grade 3-4 AEs	62 (61)	19 (39)
Death within 30 days of the last dose	1	0
Drug-related SAEs	28 (28)	3 (6)
AEs that led to discontinuation	23 (23)	10 (20)
AEs of Special Interest		
Fluid Retention	39 (39)	21 (43)
Superficial edema[a]	20 (20)	21 (43)
Pleural effusion	25 (25)	0
Other[b]	9 (9)	0
Grade 3-4 Hematologic toxicity		
Anemia	20 (20)	4 (8)
Thrombocytopenia	58 (58)	7 (14)
Neutropenia	63 (63)	19 (39)
Leukopenia	24 (24)	8 (16)

[a] Superficial edema included eye edema, eye swelling, eyelid edema, orbital edema, face edema, periorbital edema, face swelling, gravitational edema, localized edema, peripheral edema, pitting edema, genital edema, and scrotal edema

[b] Other fluid retention included edema, general edema, fluid retention, fluid overload, generalized edema, acute pulmonary edema, non-cardiogenic pulmonary edema, pulmonary edema, pulmonary congestion, pericardial effusion, cardiac tamponade, pulmonary hypertension, diastolic dysfunction, ventricular dysfunction, cardiomyopathy, congestive cardiomyopathy, ejection fraction decreased, cardiac failure, cardiac failure congestive, left ventricular failure, peritoneal effusion, and ascites

After Crossover

The safety profiles of dasatinib and imatinib after crossover were each consistent with those reported prior to crossover.

Three subjects who were initially treated with imatinib and then crossed over to receive dasatinib died after crossover (1 due to a lung infection, 1 due to progression of CML, and 1 due to cardiac failure). Two (2) of the 3 deaths were within 30 days of the last dasatinib dose. These deaths were considered by the investigator not to be related to dasatinib.

CONCLUSIONS:

- Dasatinib 70 mg BID was effective in inducing MCyR and CCyR after 12 weeks of treatment in subjects with CP-CML resistant to imatinib 400 to 600 mg/day.
- Dasatinib was effective across a number of difficult to treat treatment subgroups, including subjects who had not achieved cytogenetic response on prior imatinib therapy, and those who failed or progressed on doses ≥ 600 mg of prior imatinib.
- High dose imatinib 800 mg/day achieved some additional efficacy in subjects with CP-CML resistant to imatinib 400 to 600 mg/day.
- Treatment with dasatinib prolonged time to treatment failure and progression-free survival illustrating the benefit of treatment with dasatinib in this patient population.
- After crossover, subjects who crossed over from imatinib to dasatinib had high response (CHR and MCyR) rates.
- Dasatinib had an acceptable safety profile.

DATE OF REPORT: 06-Mar-2008