SYNOPSIS

Final Clinical Study Report for Study CA180043

TITLE OF STUDY: An open-label, randomized study of dasatinib vs high-dose (800 mg) imatinib in the treatment of subjects with chronic phase chronic myeloid leukemia (CP CML) who have had a suboptimal response after at least 3 months of therapy with 400 mg imatinib.

PURPOSE: The purpose of this study was to compare the rate of major molecular response (MMolR) of dasatinib (100 mg once daily [QD]) to high-dose imatinib (400 mg twice daily [BID]) therapy in CP CML subjects with a suboptimal response after at least 3 months of therapy with imatinib 400 mg once daily monotherapy. The study enrollment was terminated prematurely on 05-Sep-2008 because of slow accrual. Only 32 subjects (20.5%) of the planned 156 subjects had been randomized since enrollment of the first subject on 02-Aug-2006. Hence a synoptic format was chosen for this report.

NUMBER OF SUBJECTS: A total of 156 subjects were planned to be randomized in a 2:1 ratio, with 104 subjects in the dasatinib group and 52 subjects in the imatinib group. However, at the time of enrollment closure, 32 subjects had been randomized, with 19 subjects in the dasatinib group and 13 subjects in the imatinib group.

DISPOSITION, DEMOGRAPHICS AND OTHER PERTINENT BASELINE CHARACTERISTICS:

Subject disposition is presented in the table below.

Subject Disposition

	Number of Subjects (%)		
	Dasatinib	Imatinib	Total
	N = 19	N = 13	N = 32
All randomized	19 (100.0)	13 (100.0)	32 (100.0)
Treated	19 (100.0)	13 (100.0)	32 (100.0)
Discontinued study (treatment) during first year	8 (42.1)	10 (76.9)	18 (56.3)
Completed treatment	5 (26.3)	3 (23.1)	8 (25.0)
Other[a]	2 (10.5)	4 (30.8)	6 (18.8)
Adverse event unrelated to study drug	1 (5.3)	0	1 (3.1)
Investigator request	0	1 (7.7)	1 (3.1)
Study drug toxicity	0	1 (7.7)	1 (3.1)
Subject request	0	1 (7.7)	1 (3.1)
Discontinued study (treatment) during long-term extension	11 (57.9)	3 (23.1)	14 (43.8)
Other[b]	9 (47.4)	2 (15.4)	11 (34.4)
Completed treatment	2 (10.5)	1 (7.7)	3 (9.4)

[a] Other includes: Study termination by BMS, lost to follow-up, enrollment failure (ineligibility).

[b] Other includes: No major molecular response obtained at month 12, withdraw consent, study termination by BMS.

Baseline demographics for randomized subjects are presented in the table below.

Baseline Demographics - Randomized subject

	Dasatinib N = 19	Imatinib N = 13	Total N = 32
Age (Years)			
Mean (SD)	45.5 (14.83)	53.2 (14.24)	48.6 (14.85)
Min, Max	20, 71	29, 80	20, 80
Gender, n (%)			
Male	13 (68.4)	10 (76.9)	23 (71.9)
Female	6 (31.6)	3 (23.1)	9 (28.1)
Race, n (%)			
White	18 (94.7)	13 (100.0)	31 (96.9)
Black/African American	1 (5.3)	0	1 (3.1)
PS (ECOG), n (%)			
0	17 (89.5)	12 (92.3)	29 (90.6)
1	1 (5.3)	1 (7.7)	2 (6.3)
Not reported	1 (5.3)	0	1 (3.1)

Note: PS = Performance status SD: Standard deviation, Min: minimum, Max: maximum.

SUMMARY OF SAFETY RESULTS:

The overall safety summaries are listed in the table below.

Overall safety summary

	Number (%) of subjects	
	Dasatinib (N = 19)	Imatinib (N = 13)
Deaths	0	0
Any adverse events (AEs)	18 (94.7)	12 (92.3)
Drug-related AEs	15 (78.9)	12 (92.3)
Grade III/IV drug related AEs	1 (5.3)	4 (30.8)
Serious Adverse Events (SAEs)-regardless of relationship	3 (15.8)	1 (7.7)
Drug-Related SAEs	1 (5.3)	1 (7.7)
AEs leading to Discontinuation	1 (5.3)	1 (7.7)

There were no deaths reported in this study. Adverse events (AEs) were reported in 18 (94.7%) subjects in the dasatinib group and 12 (92.3%) subjects in the imatinib group. Drug-related AEs were reported in 15 (78.9%) subjects in the dasatinib group and 12 (92.3%) subjects in the imatinib group. The most common drug related AEs (reported in ≥ 20 %) in the dasatinib group were headache 7 (36.8 %) subjects, fatigue 6 (31.6 %) subjects and diarrhea 5 (26.3%) subjects. These events were ≤ grade 2. The most common drug related AEs reported in imatinib group were nausea 7 (53.8%) subjects, diarrhea 3 (23.1%) subjects, vomiting 3 (23.1%) subjects, asthenia 3 (23.1%) subjects, fatigue 3 (23.1%) subjects and muscle spasm 3 (23.1%) subjects. These events were ≤ grade 3.

Serious adverse events (SAEs) were reported in 3 (15.8%) subjects in the dasatinib group and 1 (7.7 %) subject in the imatinib group. Drug- related SAEs were reported in 1 (5.3%) subject in dasatinib group and 1 (7.7 %) subject in imatinib group. There were no grade 2 events noted in dasatinib group. One subject in imatinib group was noted with hematemesis and melena (both grade 2).

One subject ([redacted]) in dasatinib group was noted with grade 3 pneumonia on Day 277. Treatment was provided and the study therapy was interrupted due to the event. The event of pneumonia resolved on Day 291. The event of pneumonia was considered as possibly related to the study therapy.

One subject ([redacted]) in imatinib group was noted with hematemesis and melena (both grade 2) on Day 138. Treatment was provided and the study therapy was interrupted due to the events. The events of hematemesis and melena resolved on Day 139. The events of hematemesis and melena were considered as probably related to the study therapy.

Adverse events leading to discontinuation were reported in 1 (5.3%) subject in the dasatinib group and 1 (7.7%) subject in the imatinib group. One subject ([redacted]) was noted with grade 4 breast cancer in dasatinib group which was continuing at the time of the report. The study therapy was discontinued due to the event. The event of grade 4 breast cancer was considered as not related to the study therapy. One subject ([redacted]) was noted with dyspnea and orthopnea (both grade 4) and grade 3 oedema in imatinib group. Treatment was provided for these events. These events resolved after 26 days. The events of dyspnea, orthopnea and oedema were considered as probably related to the study therapy.

None of the subjects in dasatinib or imatinib group had a change in white blood count (WBC) count, platelet count, serum calcium level, and serum magnesium level by more than 2 grades. Absolute neutrophil count (ANC) worsened by 2 grades in 1 subject ([redacted]) in dasatinib group. This subject was noted with grade 0 ANC on Day 8 (baseline), which worsened to grade 1 on Day 169 and further worsened to grade 2 on Day 552. Serum phosphate level worsened by 2 grades in 1 subject ([redacted]) in imatinib group. This subject was noted with grade 0 hypophosphatemia on Day 10 which worsened to grade 2 on Day 16 and further worsened to grade 3 on Day 26.

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