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DASATINIB

Final Clinical Study Report for Study CA180085

Phase II Study of Dasatinib (BMS-354825) for Androgen-Deprived Progressive Prostate Cancer

Indication:	Progressive Prostate Cancer
Phase:	Phase 2
Study Initiation Date:	25-Jan-2006
Study Completion Date:	23-Dec-2008 (for the primary analysis)
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THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH GOOD CLINICAL PRACTICE

Sponsor's Responsible Medical Officer:
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Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product: SPRYCEL		
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SYNOPSIS

Final Clinical Study Report for Study CA180085

TITLE OF STUDY: Phase II Study of Dasatinib (BMS-354825) for Androgen-Deprived Progressive Prostate Cancer

INVESTIGATORS/STUDY CENTERS: A total of 95 subjects were treated at 12 sites worldwide in 3 countries: France, Italy, and USA.

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 25-Jan-06

Study Completion Date:
Last Subject Last Visit: 23-Dec-08 (for the primary analysis)

CLINICAL PHASE: Phase 2

OBJECTIVES:

Primary objective was to estimate the response rate of adding dasatinib to ongoing androgen deprivation with luteinizing hormone releasing hormone (LHRH) treatment or surgical castration.

The secondary objectives included: 1) to describe prostate specific antigen (PSA) response rate, and changes in PSA velocity and PSA doubling time of subjects receiving dasatinib, 2) to describe tumor response, bone scan response, duration of PSA response, and time to disease progression, 3) to assess safety and tolerability of dasatinib in combination with a LHRH agonist as a function of dose, and identify a well-tolerated dose in this setting, 4) to assess changes in markers of bone loss, serum alkaline phosphatase (bone-specific isoenzyme) and urinary N-telopeptide (uNTx) during dasatinib treatment, 5) to obtain pharmacokinetic (PK) data, and 6) to assess disease related symptoms using the 8 item FACT Advanced Prostate Symptom Index (FAPSI-8).

METHODOLOGY: CA180085 was an open-label, Phase 2 study of dasatinib in subjects with castrate resistant prostate cancer (CRPC). Dasatinib was administered orally, twice-daily (BID) at a dose of 100 or 70 mg BID or once-daily (QD) at a starting dose of 100 mg. Initially, 100 mg BID was administered for a total daily dose (TDD) of 200 mg; however, this was later decreased by protocol amendment to 70 mg BID, for a TDD of 140 mg, in subsequent subjects. Dasatinib dose was reduced, interrupted or stopped, as required for toxicity. Adverse events were recorded continuously. Levels of PSA were recorded within 2 weeks of first study drug administration and every 4 weeks. Assessments of bone alkaline phosphatase (BAP) and uNTx were performed along with PSA assessments. Tumor assessments (magnetic resonance imaging [MRI] or computer topography [CT]) and bone scans were performed at baseline and once every 12 weeks (and end of treatment if not performed in prior 6 weeks).

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NUMBER OF SUBJECTS (Planned and Analyzed): A total of 55 subjects were to be enrolled for each group (QD and BID) to achieve 50 response-evaluable subjects per group. In the first stage, 29 subjects were treated in each group. The second subject in the BID group and fifth subject in the QD group had stable disease (SD). Therefore the design criteria for opening the second stage was satisfied and additional subjects were enrolled. A total of 130 subjects were enrolled over the course of the study. Ninety-five subjects were treated (QD: 48 subjects, BID: 47 subjects); of these, 86 subjects were response-evaluable (43 subjects in each treatment group) for at least one of the three components (PSA response, tumor evaluation, and/or bone scan evaluation) of the composite endpoint.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Men (≥ 18 years of age) with histologically or cytologically proven prostate cancer and progressive disease based on rising PSA with either progression during first line antiandrogen therapy (AAT) (orchiectomy or LHRH agonist); or progression despite multiple hormonal therapies including AAT. Subjects must have had evidence of metastatic disease documented by transaxial imaging or radionuclide bone scan. Subject's castrate levels of serum testosterone (< 50 ng/dL) had to be determined within 2 weeks prior to starting treatment. Subjects who received an antiandrogen or adrenal androgen production inhibitors aminoglutethamide or ketoconazole as part of their prior hormonal therapy must have shown progression of disease off of the antiandrogen or androgen production inhibitors prior to enrollment.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: In the BID group, dasatinib was administered orally initially at 100 mg BID, and decreased by protocol amendment to 70 mg BID. In the QD group, dasatinib was administered orally QD at a starting dose of 100 mg. Subjects continued to receive study drug as long as tolerated or until progressive disease.

Dasatinib 20 mg tablet	Dasatinib 50 mg tablet
5E01546	5H01127 / 5G4302Z
5E01547	5K09694 / 5J4324Z
	5K09695 / 5J4325Z

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

CRITERIA FOR EVALUATION:

Efficacy: The primary study endpoint was the response rate as an indication of anti-tumor efficacy. A subject was considered to be a responder if they met one or more of the following conditions; confirmed PSA response, confirmed improved bone scan radionuclide assessment, or SD or confirmed complete response (CR) or confirmed partial response (PR) based on the evaluation of target lesions by Response Criteria in Solid Tumors [RECIST]. Tumor response assessments were based on MRI or CT scans. The response rate was defined as the proportion of all treated subjects that were responders (based on the above composite definition of response). Key secondary efficacy endpoints were duration of PSA response, responses by bone scan or other individually-appropriate radiographic measure, and time to disease progression. Bone turnover markers (BAP and uNTx) were assessed in comparison with baseline values and classified as increase, decrease, or no change.

Safety: Adverse events (AEs) were coded by MedDRA (version 11.1) system organ classes and preferred terms. Toxicities and laboratory tests were graded using the National Cancer Institute - Common Toxicity Criteria (NCI-CTC) version 3.0. Adverse events of special interest defined by the medical monitor were summarized. Drug-related AEs and serious adverse events (SAEs) were reported by initial dose level (70 mg and 100 mg) for the BID group. Laboratory tests that were not covered by the NCI-CTC grading system

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were summarized according to the following categories: below normal limits, within normal limits and above normal limits. Disease related symptoms were evaluated using the 8-item FACT FAPSI-8.

Pharmacokinetics (PK): Blood samples were collected for the plasma concentration versus time data from this study. Plasma samples were obtained for PK assessment at Week 2 (any Day 8 through 15) and were repeated at either Week 6 (approximately Day 42) or Week 8 (approximately Day 56) from subjects in both treatment groups (QD and BID).

Pharmacodynamics (PD): Blood samples were collected for vascular endothelial growth factor (VEGF), Collagen IV, and urokinase-type plasminogen activator (uPA) levels in plasma. Samples were obtained at Week 2 of treatment (any day between 8 and 15, and again at either Week 6 (approximately Day 42) or Week 8 (approximately Day 56) from subjects in both treatment groups (QD and BID).

STATISTICAL CONSIDERATIONS: The study used a modified Gehan two-stage design for both the BID and QD groups. For each group, in the first stage, data from 29 response-evaluable subjects were evaluated. If no responses had been observed, the study would have closed to accrual with the conclusion that the true response rate was unlikely to be ≥ 10% in the corresponding group. Otherwise, if there was at least 1 response, 21 additional subjects were to be enrolled. With this design there was a < 5% chance of stopping after the first stage if the true response rate was ≥ 10%. With a total accrual of 50 response-evaluable subjects the maximum width of the 95% confidence interval (CI) was 25% when the expected response rate was in the expected 10% to 30% range for the entire sample of 50 subjects. It was assumed that some subjects would not be evaluable for response. Assuming a 10% in-evaluability rate, a total of 55 subjects were to be enrolled for each group if accrual continued after the first stage.

The response rate was defined as the proportion of all treated subjects that were responders. A subject was considered to be a responder if they met one or more of the following conditions (referred to as composite response rate): confirmed PSA response, confirmed improved bone scan radionuclide assessment, SD or confirmed CR or confirmed PR based on modified RECIST criteria. A two-sided 95% exact CI for the response rate was reported. Subjects who achieved more than one type of response were counted only once. The secondary endpoints included assessment of the time to disease progression and the duration of PSA response. The time to disease progression was estimated by the Kaplan-Meier product-limit method. A two-sided 95% CI for the median time to progression and the median duration of response were assessed using the method of Brookmyer-Crowley. The proportion of subjects with an increase, decrease, or no change in values of bone metabolism markers, after at least 6 weeks of therapy were tabulated. Results were provided for all treated subjects, by dosing schedule and subsets characterized by concomitant bisphosphonate use (+ or -). Kaplan -Meier plots for time to uNTx response and duration of uNTx response along with time to BAP normalization and duration of BAP normalization were provided.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics: A total of 130 subjects were enrolled, 95 entered the treatment period and received at least 1 dose of dasatinib (QD: 48 subjects and BID: 47 subjects). Eight subjects were on-study at the time of database lock (7 in the QD group and 1 in the BID group). Reasons for discontinuations in 87 subjects who were off-study at the time of database lock are described in Table 1. Of the 47 treated subjects in the BID group, 25 subjects received 100 mg and 22 subjects 70 mg of dasatinib as their starting doses.

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Table 1: Subject Disposition

	Number of Subjects (%)		
	QD	**BID**	**Total**
Subjects Treated	48 (100.0)	47 (100.0)	95 (100.0)
On Study (1)	7 (14.6)	1 (2.1)	8 (8.4)
Off Study (1)	41 (85.4)	46 (97.9)	87 (91.6)
Reason Off Study (1)			
DISEASE PROGRESSION	28 (58.3)	33 (70.2)	61 (64.2)
STUDY DRUG TOXICITY	5 (10.4)	7 (14.9)	12 (12.6)
OTHER	4 (8.3)	1 (2.1)	5 (5.3)
SUBJECT WITHDREW CONSENT	0	4 (8.5)	4 (4.2)
ADVERSE EVENT UNRELATED TO STUDY DRUG	1 (2.1)	1 (2.1)	2 (2.1)
DEATH	1 (2.1)	0	1 (1.1)
MAXIMUM CLINICAL BENEFIT	1 (2.1)	0	1 (1.1)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	1 (2.1)	0	1 (1.1)

(1) Percentage is based on subjects treated in the respective treatment schedules

Demographic and the baseline characteristics were similar between the QD and the BID group (Table 2). The age of the study population ranged from 47 to 87 years and 70 (73.7%) subjects were ≥ 65 years. Most subjects were white (95.8%).

Table 2: Demographic Characteristics - All Treated

	Number of Subjects (%)		
	QD	**BID**	**TOTAL**
AGE			
N	48	47	95
MEAN	68.2	69.7	68.9
MEDIAN	68.0	70.0	69.0
MIN , MAX	47 , 85	54 , 87	47 , 87
AGE CATEGORIZATION (%)			
< 65	12 (25.0)	13 (27.7)	25 (26.3)
>= 65	36 (75.0)	34 (72.3)	70 (73.7)
NOT REPORTED	0	0	0
GENDER (%)			
MALE	48 (100.0)	47 (100.0)	95 (100.0)
NOT REPORTED	0	0	0
RACE (%)			
WHITE	46 (95.8)	45 (95.7)	91 (95.8)
BLACK/AFRICAN AMERICAN	1 (2.1)	2 (4.3)	3 (3.2)
OTHER	1 (2.1)	0	1 (1.1)
NOT REPORTED	0	0	0
ETHNICITY (%)			
HISPANIC/LATINO	2 (4.2)	0	2 (2.1)
NOT HISPANIC/LATINO	31 (64.6)	31 (66.0)	62 (65.3)
NOT REPORTED	15 (31.3)	16 (34.0)	31 (32.6)

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Efficacy Results:

Primary Efficacy Endpoint:

Out of the 95 treated subjects, 25 (26.3%) subjects were responders, ie, had a composite response based on meeting one or more of the following criteria. Subjects who achieved more than one type of response were counted only once.

- Confirmed PSA response (decrease in PSA value ≥ 50% from baseline for 2 successive evaluations, at least 2 weeks apart, for a total of 3 measurements) was observed in 2 subjects, 1 in the QD and 1 in the BID group
- Tumor response of SD (based on RECIST) was observed in 22 (23.2%) treated subjects; 10 in the QD group and 12 subjects in the BID group and PR was observed in 1 subject in the QD group
- Confirmed improved bone scan (disappearance of at least 1 lesion, no new lesions appearing since the most recent prior assessment, and new pain not developing in an area that was previously visualized, confirmed on 2 examinations at least 4 weeks apart) was observed in 1 subject in the BID group

The subject in the BID group who had a confirmed PSA response also had confirmed improved bone scan and was counted only once as a responder.

The composite response rates were similar in subjects who received either 70 mg or 100 mg BID as their starting dose (22.7% and 32.0%, respectively). Similarly, the composite response rate in the QD group was 25.0%.

Secondary Efficacy Endpoints: Results for the secondary endpoints of PSA response**,** tumor response (RECIST), and bone scan assessments are presented for response evaluable subjects in Table 3. All subjects who had at least 2 on-study valid PSA measurements were considered PSA response-evaluable. All subjects who had at least 1 measurable lesion at baseline and at least 1 on-study tumor assessment were considered tumor response-evaluable. All subjects who had at least 1 on-study valid bone scan measurements were considered bone scan response-evaluable.

Table 3: Secondary Efficacy Endpoints - Response-Evaluable Subjects

	Number (%) of Subjects		
	QD N=43	BID N=43	Total N=86
PSA Response			
PSA Response (1)			
Response Rate	1/43 (2.3)	1/43 (2.3)	2/86 (2.3)
Duration of PSA Response (months)			
	N = 1	N = 1	
	0.82	11.72	NA
PSA Velocity	N = 43	N = 43	N = 86
Median	0.2	0.4	0.3
Min-Max	-0.4- 5.7	-0.2 - 13.2	-0.4 - 13.2
Decreased	25 (58.1)	16 (37.2)	41 (47.7)
PSA Log Slope	N = 43	N = 43	N = 86
Median	0.005	0.007	0.006
Min-Max	-0.015 - 0.018	-0.008 - 0.029	-0.015 - 0.029
Decreased	38 (88.4)	34 (79.1)	72 (83.7)

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Table 3: Secondary Efficacy Endpoints - Response-Evaluable Subjects

	Number (%) of Subjects		
	QD N=43	BID N=43	Total N=86
PSA Doubling Time	N = 38	N = 41	N = 79
Median	130.5	94.9	109.9
Min-Max	39-858	24-2622	24 - 2622
Increased	34 (89.5)	32 (78.0)	66 (83.5)
Tumor Response by RECIST			
Overall Tumor Response	N = 18	N = 21	N = 39
Complete Response (CR)	0 (0.0)	0 (0.0)	0 (0.0)
Partial Response (PR)	1 (5.6)	0 (0.0)	1 (2.6)
Stable Disease (SD) (2)	10 (55.6)	12 (57.1)	22 (56.4)
Progressive (PD)	7 (38.9)	9 (42.9)	16 (41.0)
Stable Disease (at least 12 weeks)	9/18 (50.0)	11/21 (52.4)	20/39 (51.3)
Radiographical Disease Control Rate (CR+PR+SD)	11/18 (61.1)	12/21 (57.1)	23/39 (59.0)
Bone Scan Assessment			
Radionuclide Bone Scan Assessment (3)			
Improved*	1 (2.5)	1 (2.6)	2 (2.6)
Stable**	27 (67.5)	22 (57.9)	49 (62.8)
Progression	12 (30.0)	15 (39.5)	27 (34.6)
Confirmed Improved Radionuclide Bone Scan***	0/40 (0.0)	1/38 (2.6)	1/78 (1.3)

Percentages are based on response evaluable subjects.
Results include data up to the off-treatment date plus seven days.
Confidence limits were computed using Clopper-Pearson method
PSA doubling time was summarized for subjects that had positive PSA doubling time at baseline and on-study.
(1) PSA response evaluable subjects have at least 2 on-study PSA measurements.
(2) Stable disease for any duration.
(3) Radionuclide bone scan response evaluable subjects have at least 1 on-study bone scan assessments.
* at least 1 lesion disappeared, no new lesions appeared since the most recent prior assessment, and new pain did not develop in an area that was previously visualized.
** no new lesions appeared at the subsequent 12 week assessments, or that new pain had not developed in an area that was previously visualized.
*** the response was noted on 2 examinations at least 4 weeks apart

Changes in Bone Turnover Markers

uNTx: In the QD group, the median percent (maximum) decrease from baseline in uNTx in subjects taking bisphosphonates (N = 9) was 50.0% (range: 31.0% to 80.0%) and in subjects not taking bisphosphonate (N = 24) was 47.6% (range: 10.0% to 89.0%). In the BID group, the median percent (maximum) decrease from baseline in uNTx in subjects taking bisphosphonates (N = 16) was 55.3% (range: 15.0% to 74.0%) and in subjects not taking bisphosphonates (N = 17) was 43.3% (range: 4.0% to 86.0%).

BAP: In the QD group, the median percent (maximum) decrease from baseline in BAP in subjects taking bisphosphonates (N = 7) was 16.7% (range: 6.0% to 88.0%) and in subjects not taking bisphosphonate

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(N = 19) was 28.0% (range: 6.0% to 68.0%). In the BID group, the median percent (maximum) decrease from baseline in BAP in subjects taking bisphosphonates (N = 13) was 20.0% (range: 4.0% to 35.0%) and in subjects not taking bisphosphonate (N = 12) was 29.5% (range: 4.0% to 62.0%).

Disease Progression: In the QD group, 30 of the 48 (62.5%) treated subjects and in the BID group, 34 of the 47 (72.3%) treated subjects had disease progression while on study. The median time to disease progression was 4.7 months (95% CI: 2.8 - 5.5) in the QD group and 2.8 months (95% CI: 2.8 - 5.4) in the BID group.

Prostate Cancer Symptoms: The FAPSI-8 score decreased from baseline in both treatment groups (QD and BID). Lower FAPSI score indicates more symptoms. However, there was no applicable difference in the score from baseline and end of treatment.

Safety Results: Drug-related SAEs, AEs leading to discontinuation, drug-related AEs, and AEs of special interest were analyzed for the QD (ie, subjects receiving 100 mg daily) and for the two BID groups (ie, subjects receiving either 70 or 100 mg BID). The overall safety profile was similar between the two BID (70 mg and 100 mg) treatment groups; therefore safety data presented are mostly for the combined BID group**.**

No new safety concerns were identified with dasatinib administered as QD or BID in this study population. A total of 4 deaths were reported; none were attributed to study drug toxicity. The 2 deaths reported in the QD group occurred within 30 days of last dose of dasatinib and in the BID group post 30 days of last dose of dasatinib. In both treatment groups, pleural effusion was the most common drug-related AE leading to discontinuation; however, no drug-related Grade 4 AEs were reported that lead to discontinuation. Drug-related Grade 3 or 4 AEs and drug-related SAEs were lower in the QD group than in the combined BID group though the median duration of study therapy was a month longer in the QD group than the BID group and dose reductions were not allowed in the QD group.

Adverse events of special interest such as diarrhea, pleural effusion, nausea, dyspnea, rash, headache, asthenia, superficial edema, pericardial effusion, and flushing were lower in the QD than the BID group (Table 4).

On-study laboratory abnormalities (hematology, liver function, renal function, electrolytes, platelets, and urinalysis) were mostly mild to moderate. Only 3 subjects in the BID group had worsening of hematological parameters to Grade 3 and 1 subject in the QD group had a transient on-study Grade 4 hypocalcemia (Table 4).

Table 4: Safety Summary for Treated Patients

	Number (%) of Subjects	
	QD (100 mg) N = 48	**BID (70 mg and 100 mg) N = 47**
All Deaths	2 (4.2)	2 (4.3)
Drug-related SAEs	3 (6.3)	6 (12.8)
Drug-related AEs Leading to Discontinuation	6 (12.5)	7 (14.9)
All AEs	48 (100.0)	47 (100.0)
Drug-related AEs	43 (89.6)	47 (100.0)
Drug-related Grade 3/4 AEs	6 (12.5)	15 (31.9)
AEs of special interest*		
Diarrhea	13 (27.1)	29 (61.7)
Pleural Effusion	9 (18.8)	24 (51.1)
Nausea	13 (27.1)	22 (46.8)
Dyspnea	11 (22.9)	19 (40.4)

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Table 4: Safety Summary for Treated Patients

	Number (%) of Subjects	
	QD (100 mg) N = 48	**BID (70 mg and 100 mg) N = 47**
Rash	8 (16.7)	19 (40.4)
Headache	13 (27.1)	18 (38.3)
Asthenia	9 (18.8)	13 (27.6)
Superficial edema	5 (10.4)	12 (25.5)
Pericardial effusion	1 (2.1)	11 (23.4)
Flushing	3 (6.3)	10 (21.3)
On-study Laboratory Abnormalities		
On-study Grade 3/4 Hematologic Abnormalities		
Absolute Neutrophil Count	0	1 (2.1)
Hemoglobin	0	1 (2.1)
Platelets	0	1 (2.1)
Leukocytes	0	0
Hypocalcemia	1 (2.1)	0

* Adverse events of special interest (drug-related AEs) defined by Bristol-Myers Squibb (BMS) medical monitor were summarized by preferred term (MedDRA Version 11.1).

Pharmacokinetic Results: Out of 1, 3, and 6 h time points, mean plasma concentration was maximum at 1 hour for all doses and treatments. The mean (± SD) plasma concentrations for 100 mg QD at 1 hour were 102.98 ng/mL (± 81.80 ng/mL) and 89.55 ng/mL (± 78.64 ng/mL) for Week 2 and Week 6 treatments, respectively. The mean (± SD) plasma concentrations for 100 mg BID at 1 hour were 73.05 ng/mL (± 64.51 ng/mL) and 59.75 ng/mL (± 35.86 ng/mL) for Week 2 and Week 6 treatments, respectively. Similarly, mean (± SD) plasma concentrations for 70 mg BID at 1 hour were 66.47 ng/mL (± 43.94 ng/mL) and 77.83 ng/mL (± 55.72 ng/mL) for Week 2 and Week 6 treatments, respectively.

Pharmacodynamic Results: Analyses of VEGF, Collagen type IV and uPA data will be presented in a separate report.

CONCLUSIONS:

- Efficacy results demonstrate dasatinib's activity as evaluated by PSA, RECIST measurable disease and stabilization of bone. Additionally, dasatinib has shown an effect on bone turnover (as measured by uNTx and BAP). This confirms the potential dual effect of dasatinib on both prostate tumors (visceral/nodal) and bone turnover/metabolism including osteoclast activity.
- Based on the overall safety including fewer drug-related Grade 3 or 4 AEs and SAEs, (which were lower in the QD group compared with the BID combined group), 100 mg QD of dasatinib is considered as the tolerable and relevant dose in this patient population.

DATE OF REPORT: 26-Jun-2009

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