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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® | | |
| Name of Active Ingredient: Dasatinib | | |

# SYNOPSIS

## Addendum 01 to 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 the United States of America.

**PUBLICATIONS:**

Yu EY, Wilding G, Posadas E. Phase II study of dasatinib in patients with metastatic castration-resistant prostate cancer. Clin Cancer Res. 2009; 15:7421-7428.

**DATABASE LOCK FOR THIS ADDENDUM:** 09-Dec-2010

**CLINICAL PHASE:** 2

**OBJECTIVES:** The 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 data, and 6) to assess disease related symptoms using the 8 item FACT Advanced Prostate Symptom Index.

**PURPOSE OF ADDENDUM:** This addendum to the clinical study report (CSR) includes updated on-study and follow-up safety data through a last subject last visit date of 18-Oct-2010. As of the original CSR, 8 subjects were still on treatment; all subjects were off treatment and off follow-up as of this addendum.

**METHODOLOGY:** CA180085 was an open-label, Phase 2 study of dasatinib in subjects with castrate-resistant prostate cancer. 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. A further protocol amendment reduced the dose further to 100 mg QD. Dasatinib dose was reduced, interrupted or stopped for toxicity, as required. Adverse events were recorded continuously.

**NUMBER OF SUBJECTS (Planned and Analyzed):** Of 130 subjects enrolled, 95 subjects were treated (QD [100 mg]: 48 subjects, BID [70 or 100 mg]: 47 subjects).

**DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:** See final CSR (dated 26-Jun-2009).

**TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS:** See final CSR.

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

**CRITERIA FOR EVALUATION:** See final CSR.

**STATISTICAL CONSIDERATIONS:** See final CSR.

**SUMMARY OF RESULTS:**

**Subject Disposition:**

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

**Table 1: Subject Disposition**

| | Number of Subjects (%) | | |
|---|---|---|---|
| | QD | BID | Total |
| Subjects Treated | 48 (100.0) | 47 (100.0) | 95 (100.0) |
| On Study (1) | 0 | 0 | 0 |
| Off Study (1) | 48 (100.0) | 47 (100.0) | 95 (100.0) |
| Reason Off Study (1) | | | |
| DISEASE PROGRESSION | 33 ( 68.8) | 34 ( 72.3) | 67 ( 70.5) |
| STUDY DRUG TOXICITY | 6 ( 12.5) | 7 ( 14.9) | 13 ( 13.7) |
| 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) |
| SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT | 2 ( 4.2) | 0 | 2 ( 2.1) |
| DEATH | 1 ( 2.1) | 0 | 1 ( 1.1) |
| MAXIMUM CLINICAL BENEFIT | 1 ( 2.1) | 0 | 1 ( 1.1) |

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

**Baseline/Demographic Characteristics:** See final CSR.

**Efficacy Results:** See final CSR.

**Safety Results:** No new safety concerns were identified with dasatinib administered as QD or BID in this study population (Table 2). 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 the 2 deaths in the BID group were reported 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, and the median duration of study therapy was a month longer in the QD group than the BID 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 group.

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 (Table 2). One subject in the QD group had a transient on-study Grade 4 hypocalcemia.

**Table 2: 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 | 1 (2.1) | 6 (12.8) |
| Drug-related AEs Leading to Discontinuation | 9 (18.8) | 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 | 7 (14.6) | 15 (31.9) |
| AEs of special interest* | | |
| Diarrhea | 13 (27.1) | 29 (61.7) |
| Pleural Effusion | 10 (20.8) | 24 (51.1) |
| Nausea | 14 (29.2) | 22 (46.8) |
| Dyspnea | 13 (27.1) | 19 (40.4) |
| 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 |

* 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).

**CONCLUSIONS:** Unchanged from the final CSR. These conclusions were:

- 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:** 04-Apr-2011