SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: VELCADE™ for injection NAME OF ACTIVE INGREDIENT: Bortezomib	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: 26866138-MMY-3001 **Title of Study:** An International Single-Arm Protocol to Provide Expanded Access to VELCADE™ for Patients With Multiple Myeloma Who Have Received at Least Two Previous Lines of Therapy and are Refractory to or Have Relapsed After Their Last Therapy for Multiple Myeloma		
Study Initiation/Completion Dates: 17 May 2004 - 14 August 2006		**Phase of development:** 3b
Objectives: The primary objective was to provide VELCADE to patients with multiple myeloma who had received at least 2 previous lines of therapy[1] and were refractory to or had relapsed after their last therapy. The secondary objectives were to assess the safety and tolerability of VELCADE and to follow monoclonal paraprotein (M-protein) levels in patients receiving VELCADE as a measure of disease burden.		
Methodology: This was an international, multicenter, open-label, single-arm, noncomparative study. After providing written informed consent, patients were evaluated for eligibility during a screening period of 21 days (Days –21 to –1). In total, 628 patients previously diagnosed with multiple myeloma based on standard criteria, who had received at least 2 previous lines of therapy for multiple myeloma and, in the investigator's opinion, had become refractory to or relapsed after the last therapy were randomized and enrolled in the study. Eligible patients were to sign an informed consent, have a Karnofsky performance status ≥60, and meet all inclusion criteria and meet none of the exclusion criteria. Patients were treated with VELCADE for up to eight 3-week treatment cycles. If approved by the sponsor, treatment could have been extended for patients who were still responding. VELCADE was administered at the clinical center as a single, short (3 to 5 seconds) intravenous bolus on Days 1, 4, 8, and 11 of each 3-week cycle. The treatment period in each cycle was followed by a 10-day rest period (Days 12 to 21), when no study drug was administered. The starting dose of VELCADE was 1.3 mg/m^2 (the maximum dose allowed). The dose was to be reduced, withheld, or discontinued if certain toxicities occurred. Patients who experienced progressive disease after completing at least Cycle 2 or had no change from baseline (stable disease) after completing at least Cycle 4 could, at the investigator's discretion, have had oral dexamethasone 20 mg/day added to their treatment with VELCADE on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each cycle.		

[1] A line of therapy was defined as a course or schedule of therapy, e.g., melphalan and prednisone, given over a period of months on a regular basis. Conditioning treatment followed by high dose chemotherapy preceding autologous stem cell transplantation also qualified as 1 line of therapy.

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Criteria for Evaluation:

Safety was assessed by the monitoring of adverse events (AEs), physical (including neurological/peripheral neurological) examinations, vital signs measurements (blood pressure, pulse, respiratory rate, and temperature), and hematology and clinical chemistry tests. Safety analyses were to be performed on the safety population, defined as all patients who received at least 1 dose of study drug.

Response to treatment was based on changes in serum and urine M-protein levels. Response categories were evaluated based on a modified form of the South West Oncology Group criteria. Karnofsky performance status was also assessed. Efficacy analyses were to be primarily performed on the Full Analysis Set (FAS), defined as all patients who received any dose of VELCADE with at least 1 post-baseline efficacy measurement.

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SUMMARY – CONCLUSIONS

SAFETY RESULTS:

	Total (N = 638)	
Number of patients with any:	n	(%)
TEAE	608	(95.3)
Related TEAE	559	(87.6)
Serious TEAE	265	(41.5)
Related serious TEAE	145	(22.7)
Grade 3 or 4 toxicity TEAE	444	(69.6)
Related grade 3 or 4 toxicity TEAE	360	(56.4)
TEAE causing discontinuation of VELCADE	233	(36.5)
Related TEAE causing discontinuation of VELCADE	168	(26.3)
Number of patients who died due to TEAE	88	(13.8)

The overall incidence of TEAEs was high (95% of 638 subjects), which was not unexpected considering the study population and therapeutic indication in this study. The nature and incidence of TEAEs were similar to those reported in earlier studies. Thrombocytopenia (253 [40%] of 638 patients) was the most frequently reported TEAE of any toxicity, and was Grade 3 or 4 and related to treatment in 25% of 638 patients. Thrombocytopenia was the most common Grade 3 or 4 TEAE (22% and 18% of 638 patients, respectively), followed by neutropenia (Grade 3: 13% of 638 patients; Grade 4: 3% of 638 patients). Malignant neoplasm aggravated was the most frequently reported serious TEAE (44 [7%] of 638 patients) or AE that resulted in death (39 [6%] of 638 patients). VELCADE was discontinued for 233 (37%) of 638 patients as the result of a TEAE. The most frequently reported TEAE leading to discontinuation was peripheral neuropathy NOS (33 [5%] of 638 patients). Peripheral neuropathy was also the most frequently reported related TEAE leading to discontinuation (32 [5%] of 638 patients).

EFFICACY RESULTS:

All patients who received at least 1 dose of study drug and had postdose efficacy data were included in the FAS. All efficacy analyses were based on this population. In total, 613 patients were included in the FAS.

	Total (N = 613)		
Final Visit	N	(%)	95% CI
n	570		
Complete response	56	(9.8)	(7.5; 12.6)
Response	104	(18.2)	(15.2; 21.7)
Partial response	80	(14.0)	(11.3; 17.2)
Minimal response	61	(10.7)	(8.3; 13.5)
Stable disease	75	(13.2)	(10.5; 16.2)
Progression	194	(34.0)	(30.1; 38.1)

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At Cycle 3, 40% of 544 patients had at least a partial response (i.e. a reduction in M-protein of at least 50%). At Cycle 5, 51% of the remaining 420 patients had at least a partial response, and at Cycle 7, 56% of the remaining 291 patients had at least a partial response. Overall, 54% of the 602 patients with data (53% of the FAS) had at least a partial response to treatment at some time during treatment.

Of the 602 patients with data, 71 (12%) had a best response of complete response and 323 (54%) had at least a partial response to treatment. The median time to best response of at least stable disease was 63 days (range 7-235 days). The first response was most commonly stable disease (25% of 602 patients), but 233 patients (39% of 602 patients) had at least a partial response as their first response to treatment. The median time to a first response of at least stable disease was 42 days (range 7-125 days).

CONCLUSION:

In total, 638 patients with multiple myeloma, all but 8 of whom had received at least 2 previous lines of therapy and were refractory to or had relapsed after their last therapy, received VELCADE in this study.

Overall, the safety profile of VELCADE 1.3 mg/m^2 was similar to that seen previously in patients with relapsed and/or refractory multiple myeloma. Overall, 53% of these patients had at least a partial response to treatment with VELCADE. Median times to first and best response were 42 and 63 days, respectively, suggesting that prolonged treatment with VELCADE beyond the initial response may result in improved quality of response.

Date of the report: 02 May 2008

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