CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-602

MEDICAL REVIEW

CLINICAL REVIEW

NDA 21-602
VELCADE™ (bortezomib) for Injection

United States Food and Drug Administration (FDA)
Center for Drug Evaluation and Research
Division of Oncology Drug Products

Clinical NDA Review

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Executive Summary

I Recommendations

1 Recommendation on Approvability

The United States Food and Drug Administration (FDA) Division of Oncology Products (DODP) review team therefore recommends Accelerated Approval, under CFR§314.510 Subpart H, for the treatment of MM in patients who have received at least two prior therapies and have demonstrated disease progression on last therapy. Confirmation of clinical benefit may be based on an analysis of the ongoing phase 3 study 039 in MM.

In the studies under review, PS-341 demonstrated efficacy and safety in the treatment of multiple myeloma (MM) after at least 2 prior therapies. In study 025, PS-341 was administered at a 1.3 mg/m2/dose intravenously twice weekly for two out of three weeks for up to 8 cycles to 202 patients with MM who had received at least two prior therapies and demonstrated disease progression on last therapy. Fourteen patients were excluded from the analysis. In the 188 patients in the final analysis population, a complete response (CR) rate of 2.6% (n=5) and a partial response (PR) rate of 27% (n= 52) was demonstrated. Supportive evidence of efficacy was provided by a small phase 2 dose-ranging study in MM, in which 54 patients who had received at least two prior therapies received either a 1.0 mg/m2/dose or a 1.3 mg/m2/dose twice weekly for two out of three weeks. A single complete response was seen in each dose cohort, and an overall 30% (8/27) CR+PR rate at 1.0 mg/m2 and a 38% (10/26) CR+PR rate at 1.3 mg/m2 was noted. Durable complete responses may be considered to be evidence of clinical benefit.[1] Blade criteria for complete response have not yet been validated as evidence of clinical benefit, particularly outside the context of transplantation, but there is sufficient support in the literature to suggest that these criteria are a surrogate, 'reasonably likely to predict' clinical benefit. Based on a literature review and the advice of practitioner consultants, the partial response rate was also considered to be a surrogate for clinical benefit. The sponsor performed additional clinical benefit analyses of the patients exhibiting a partial response to further support the concept that these patients benefited from treatment with PS-341.

Safety evaluation is adequate for approval for this indication. The safety database is comprised of 379 patients with advanced, previously treated malignancies from six studies, five where VELCADE was used alone and one study in combination with gemcitabine. The pharmacokinetics of VELCADE as monotherapy has not been fully characterized. Metabolism is primarily by liver enzymes. Principal toxicities (adverse events) at the 1.3 mg/m2 twice weekly schedule include asthenia (65%), nausea (64%), diarrhea (51%), anorexia (43%), thrombocytopenia (43%), and peripheral neuropathy (37%). Severe adverse events include asthenia, thrombocytopenia, peripheral neuropathy, and neutropenia. Neuropathy is cumulative

with continued treatment; its reversibility is uncertain. Special attention should continue to focus on (1) uncertainty regarding the degree and reversibility of cumulative neuropathy and (2) adverse cardiovascular reactions including hypotension and syncope which may be drug-related and/or influenced by the patient's underlying hydration and cardiovascular reserve. In addition, the sponsor should assist clinicians with additional education in the recognition of and dose-adjustment for non-hematologic toxicities of anti-neoplastic drugs, including reference to the NCI CTC http://ctep.info.nih.gov/reporting/ctc.html) website in promotional materials. The proposed vial size (3.5 mg) may pose a hazard if the full vial was inadvertently administered.

2 Recommendation on Phase 4 Studies and/or Risk Management Steps

The following are Phase 4 Commitments under CFR§314.510 Subpart H:

A. Clinical Phase 4 Commitments:

1) Provide complete study reports on the following ongoing studies:

   - Study 039: "An International, Multi-center, Randomized, Open-label Study of PS-341 Versus High Dose Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma"

   - Study 029: "A Phase II Open- Label, Extension Study to Provide PS- 341 to Patients Who Previously Participated in a PS- 341 Clinical Study and Who may Benefit from Re-Treatment with or Continuation of PS- 341 Therapy

2) Initiate and complete a study in previously untreated multiple myeloma patients comparing VELCADE alone, high-dose dexamethasone alone and combination of VELCADE plus high-dose dexamethasone.

3) Provide follow up information to characterize the frequency, severity, and reversibility of the peripheral neuropathy on study 025, 029, and the current VELCADE myeloma protocol study 039.

B. Non Clinical Pharmacology/Toxicology Phase 4 Commitments:

1. Additional non-clinical studies appear warranted given the undefined etiology of the cardiovascular effects seen in multiple animal studies, as well as the occurrence of cardiovascular adverse events in patients.
   - Given the narrow safety margin between the recommended clinical dose (1.3 mg/m^2) and 100 % lethality in non-clinical studies (3.0 mg/m^2 in monkeys), we recommend the sponsor determine the factors associated with PS-341 induced lethality at 12–14 hours post-dose.
   - Since PS-341 promotes dissimilar effects in monkey and mouse, future studies should be conducted in a species that most closely models the human response.

- The Sponsor should identify the cardiac cell type(s) that are most effected following PS-341 administration to provide potential clinical interventions in the event of an overdose.
- Future non-clinical studies need to incorporate neuronal assessments to identify or rule out CNS involvement in these phenomena.

2. The Sponsor should conduct a study in cells transfected with a normal PrP gene to determine if administration of PS-341 results in the accumulation of proteins in the cytosol, similar to treatment with other proteasome inhibitors such as lactacystin or epoxomicin, as reported by Ma and Lindquist, 2002. Further, determine if misfolding of the normal PrP protein occurred with the formation of proteins with a PrP^{sc}-like conformation. The implications of these findings to the possible initiation and/or exacerbation of spongiform encephalopathies should be addressed.

C. Clinical Pharmacology Phase 4 Commitments

1) You should conduct a study to characterize the Pharmacokinetics (PK) of bortezomib as a single agent at 1.3 and 1.0 mg/m^2 twice-weekly dose in at least 12 multiple myeloma patients at each dose level. Patients should have normal to mild creatinine clearance values (50 ml/min). The pharmacokinetics should be characterized both at Cycle 1 and at a subsequent cycles to address the time dependent changes in the PK of bortezomib as a single agent.

2) As bortezomib is metabolized by the liver, you should conduct a pharmacokinetic and pharmacokinetic/safety (PK and PK/Safety) study in patients with hepatic impairment to adequately provide dosing recommendations for this special patient population in the labeling for VELCADE.

3) You should conduct a study to evaluate the PK and PK/safety of bortezomib in patients with advanced malignancies and varying degrees of renal dysfunction.

4) You should conduct PK and PK/PD (pharmacokinetics/pharmacodynamics) studies to examine the potential for drug-drug interactions between bortezomib and drugs that are inhibitors (e.g., ketoconazole), or inducers (e. g., rifampin) of cytochrome P450 3A4. You should also collect adverse reactions noted in this study and evaluate any relationship between plasma levels and adverse reactions.

5) You should evaluate the contribution of cytochrome P 450 3A4, 2D6, 2C19, 2C9, and 1A2 in the metabolism of bortezomib using in vitro systems (microsomes, hepatocytes, liver tissue, etc.) Based on the results of the study, additional drug-drug interaction studies may be required.

D. Additional Suggestions (Not Phase 4 Commitments):

1) Provide the complete study report, pharmacogenomic data, and data analysis collected in study 025.
2) Consider changing the single dose vial size to minimize chance for overdose by reducing the contents to a maximum of 3.0 mg. (This represents the actual dose for a 2.30 m2 person dosed at 1.3 mg/m2 or a 2.0 m2 person dosed at 1.5 mg/m2.)
3) VELCADE appears to be more tolerable at 1.0 mg/m2 compared with 1.3 mg/m2 and there is not sufficient information on efficacy to determine a dose-response. Provide additional information on the safety and efficacy of VELCADE at a different dose, for example n initial dose of 1.0 mg/m2 in a population that may not be able to tolerate full doses. This might include elderly patients and patients with poor performance status or baseline peripheral neuropathy.

II Summary of Clinical Findings

1 Brief Overview of Clinical Program

Multiple myeloma (MM) is a malignant plasma cells disorder accounting for about 10% of hematological malignancies. MM remains a fatal disease: median overall survival does not exceed 4 years with conventional chemotherapy approaches. The disease is characterized by the clonal proliferation of plasma cells, which produce a monoclonal immunoglobulin heavy and/or light chain (paraprotein, M-protein or M-component). The measurement of this imunoglobulin in the serum or urine provides a mechanism for evaluating response to therapy.

PS-341 (VELCADE, bortezomib) is a small molecule dipepdidyl boronic acid inhibitor of the 26 S proteasome derived from leucine and phenylalanine. The precise mechanism of action is under investigation, but inhibition of the proteasome induces apoptosis of myeloma cells. The studies under review (024, 025) enrolled 256 patients with relapsed MM in 2 open-label studies. Patients were given PS-341 at a dose of either 1.0 or 1.3 mg/m2/dose, twice weekly for two out of three weeks. Patients who did not respond to PS-341 alone could be treated with the addition of dexamethasone. The primary objective was the determination of response rate. Secondary objectives were safety, response to PS-341 and dexamethasone, time to event, and an ongoing pharmacogenomic analysis.

2 Efficacy

The primary efficacy endpoint for the studies under review was response rate. The criteria for response analysis are described in detail in the protocol review section of the NDA review. Durable complete responses may be considered to be evidence of clinical benefit in hematologic malignancies, however the Blade criteria for complete response have not been validated as a clinical benefit, particularly outside the context of transplantation. CR^{Blade} criteria were initially developed to evaluate responses in the post transplant population, but more recently have also been used to evaluate efficacy in patients with myeloma undergoing treatments other than transplant. Southwest Oncology Group (SWOG) remission criteria (R^{SWOG}) have been used for many years to evaluate responses in MM. These criteria require 75% reduction in serum Myeloma protein and/or 90% reduction in urine myeloma protein. The

sponsor's definition of partial response (PR) required a 50% reduction in serum myeloma protein and 90% reduction of urine protein. $CR^{(IF+)}$ was an exploratory response criterion requiring 100% reduction of serum myeloma protein, which has not been used consistently in literature reports or validated as a clinical benefit. All responses were verified by the FDA efficacy reviewer using datasets and patient data listings and by reviewing the independent response committee (IRC) worksheets and notes. In addition, the FDA reviewers examined bone marrow aspirates and biopsies provided by the sponsor on selected patients in order to confirm complete remissions.

Study 025 included 202 patients with a diagnosis of MM using standard criteria, who had relapsed following a response to standard first-line chemotherapy [(e.g., vincristine, Adriamycin, and dexamethasone (VAD) or methylprednisolone (MP)] or first-line high-dose chemotherapy, and were refractory [i.e., failure to achieve at least CR, PR, or stable disease (SD)] to their most recent chemotherapy, whether or not containing systemic corticosteroids. The study population was quite heterogeneous in terms of prior therapy, and included 5 patients who had received only corticosteroids and biaxin or thalidomide, as well as 63 patients who had received multiple stem cell transplants. Several patients who had received various other therapies including vaccines were also included. The 5 relatively lightly pretreated patients were excluded from the FDA efficacy analysis for the indication of progression following 2 prior therapies. Protocol deviations were fairly minor. The following Table summarizes the FDA and sponsor's efficacy results for study 025:

Table 1: Efficacy Response Analyses (VELCADE monotherapy) Study M34100-025

	Sponsor N=193			FDA[a] N=188		
	N	%	95% CI	N	%	95% CI
CR^{Blade}	7	3.6%	(1%, 7%)	5	2.7%	(1%, 6%)
CR^{IF+}	12	6.2%	(3%, 11%)	12	6.4%	(3%, 11%)
R^{SWOG}	15	7.7%	(4%, 12%)	16	8.5%	(5%, 13%)
.....PR	19	9.8%	(6%, 15%)	19	10.1%	(6%, 15%)
Overall RR	53	27%	(21%, 34%)	52	27.7%	(21%, 35%)

Note: Responses subsequent to the use of dexamethasone are excluded.

[a] FDA analysis: 5 additional patients excluded for minimal pretreatment, including one CR^{Blade}.
1 additional CR^{Blade} not confirmed, pt assigned to CR^{IF+}.
One CR^{IF+} not confirmed, pt assigned to R^{Swog}

Small differences in response rates by CR^{Blade} criteria between the FDA reviewer and sponsor were due to the exclusion of 5 patients who were minimally pretreated, and from a patient whose complete response could not be confirmed by the FDA reviewer. A slightly higher response rate was observed for patients under 65 years of age (32%) as compared to patients over 65 years (19%) and in Black patients (48%) as compared to White patients (24%) or patients of other races (33%), but these results did not reach statistical significance. Response to PS-341 alone was similar in the different subtypes of myeloma, however, a decreased likelihood of response in those patients with either plasma cells >50% in the bone marrow or with abnormal

cytogenetics was observed. Five additional patients experienced a PR after the addition of dexamethasone to PS-341, but no additional CR's were reported. The median Kaplan Meier duration of overall response was 365 days including the extension studies. A small phase 2 dose-finding study (024) in which 53 patients either received the 1.0 mg/m2/dose or the 1.3 mg/m2/dose, provided additional evidence of efficacy. This study enrolled a less heavily pretreated cohort and included 5 patients who had received only corticosteroids. The sponsor's CR + PR rate was 29% in the 1.0 mg/m2 group compared with a 35% CR+PR in the 1.3 mg/m2 dose group. The FDA CR + PR rate was 23% in the 1.0 mg/m2 group compared with a 35% CR+PR rate in the 1.3 mg/m2 dose group, after exclusion of 5 less heavily pretreated patients. The numbers were too small to make conclusions regarding the comparative efficacy of the two different dose groups or for analysis of different subgroups.

Efficacy conclusions: Based on a careful review of the complete responders, including microscopic analysis of bone marrow slides by the FDA review team, complete responders were considered an improvement over available therapy. Partial response rates appeared to be similar to those previously reported with available conventional dose therapy in the relapsed and refractory population (see Table 2).

3 Safety

Clinical safety is adequate for marketing under accelerated approval for this indication. Areas of limited safety experience have been noted; concerns are expressed in the labeling and included in phase 4 commitments. Special attention should be given to (1) the uncertainty of the degree and reversibility of cumulative neuropathy with more prolonged drug exposure and (2) adverse cardiovascular reactions including hypotension and syncope which may be drug-related and/or influenced by the patients' underlying hydration and cardiovascular reserve.

The safety database is comprised of 379 patients with advanced, previously treated malignancies from six trials of VELCADE (bortezomib, PS-341). In the four phase I trials, dose escalations were conducted with once or twice weekly IV dosing schedules for two to four weeks. The two phase II trials, with a total of 256 patients with MM, used the twice weekly times two weeks schedule and represent the efficacy database for accelerated approval. Only one of the phase II studies (54 patients) included a dose range (1.0 versus 1.3 mg/m2 per dose). Clinical experience generally paralleled pre-clinical observations except that the acute cardiovascular mortality in monkeys at doses of 3.0 mg/m2 or more has not been described in humans. (Single doses of up to 2.0 mg/m^2 once per week have been administered to adults.)

In the phase II studies, among the 228 patients who received the 1.3 mg/m2 dose, the most commonly reported adverse events (AEs) were: asthenic (malaise-fatigue) conditions (65%), nausea (64%), diarrhea (51%), anorexia (43%), constipation (43%), thrombocytopenia (43%), peripheral neuropathy (37%), pyrexia (36%), vomiting (36%), and anemia (32%). Adverse events of ≥ grade 3 severity included thrombocytopenia (29%), peripheral neuropathy (14%). neutropenia (15%), asthenia (11%), anemia (9%), and diarrhea, nausea, and vomiting each were 7%.

Of the serious adverse events (SAEs) for all the phase 2 myeloma study patients, the most common were pyrexia (7%), pneumonia (7%), diarrhea (5%), vomiting (5%), dehydration (5%), and nausea (4%). In total, 48% of the 256 myeloma patients experienced one or more serious adverse events. In the phase II studies, increasing dose led to an increased incidence of neuropathy, diarrhea and vomiting but not thrombocytopenia or SAEs. Increasing duration of exposure (number of cycles of therapy) also led to an increasing prevalence of neuropathy. PK data for the proposed label dose as monotherapy is not yet available. When used in combination with gemcitabine, VELCADE accumulates on twice weekly dosing (day 11 compared to day 1). The preliminary pharmacodynamic data available does not support a dose-response or dose-toxicity relation to proteasome inhibition. Confidence intervals for results substantially overlap. Data is limited to describe the safety of VELCADE in special populations (hepatic or renal impairment patients) or in combination with other drugs or in pediatric or geriatric populations. Studies of hepatic and renal metabolism in humans should be completed to permit dosing guidance in patients with organ impairment. No cytochrome P450 interactions have yet been ascertained. Bortezomib metabolism appears to be primarily via liver enzymes.

Expectant monitoring of hemodynamic, gastrointestinal (GI) and neurologic toxicity should be emphasized. The frequency and severity of diarrhea are dose dependent. At weekly single doses above 1.5 mg/m2, orthostatic hypotension and diarrhea were dose-limiting. Since myelosuppression is not a dominant toxicity, other organ toxicities may become dose-limiting in the absence of hematologically based dose reductions. Reference to the NCI CTC (common toxicity criteria) website should be added to the label to assist oncologists in the recognition and monitoring of the less common organ toxicities (http://ctep.info.nih.gov/reporting/ctc.html). The proposed vial size may pose a hazard to human use because single doses of 3.0 mg/m2 were usually lethal in primates (monkeys). The proposed single dose, non-reusable vial contains 3.5 mg of VELCADE. This provides a 2.7 mg/m2 dose to a 1.5m2 person or 3.0 mg/m2 dose to a patient of 1.2 m2 body surface area. Alternatively, this vial size represents the appropriate dose for a 2.9m2 person at a dose of 1.3 mg/m2. The possibility of inadvertent administration of one entire vial could pose a hazard. Additional notice on the vial label could call attention to this potential hazard.

4. Dosing

Schedule: A twice-weekly schedule of PS-341 was chosen on the basis of pharmacodynamic studies in the rat and cynomolgus monkey. The twice weekly clinical dosing regimen was chosen in order to allow return of proteasome activity towards baseline between dose administrations, which appeared to improve tolerability.

Dose: The recommended dose for phase 2 trials on a twice weekly for two out of three week schedule was 1.3mg/m^2/dose based on phase 1 study data. Four DLT's occurred in a cohort that received 1.56 mg/m^2, including Grade 3 diarrhea in 3 patients and Grade 3 peripheral sensory neuropathy in 1 patient. The 1.0 mg/m^2 dose appeared to be somewhat better tolerated compared with the 1.3 mg/m^2 dose. In the clinical trials under review, (024 and 025) thirty nine percent of all patients (in 024 and 025)on the 1.3mg/m2 dose completed the study, while 67% of patients (in 024) receiving the 1.0 mg/m2 dose completed the study. Twenty three percent of 230 patients

receiving the 1.3 mg/m2 dose discontinued the drug because of an adverse event compared with 11% of patients on the 1.0 mg/m2 dose. An approximately equal number of patients discontinued the study for lack of efficacy on either dose. Forty percent of all doses were held or decreased in study 025 and over half of doses were held or decreased at the 1.3 mg/m2 dose group in study 024. In study 024, a phase 2 dose ranging study of patients with multiple myeloma, there appeared to be marginally improved efficacy at 1.3 mg/m^2/dose compared with 1.0 mg/m^2/dose. The overall response rate (ORR= CR + PR + MR) to treatment with PS-341 alone was higher at 50% (13 of 26 patients) in the 1.3 mg/m^2 dose group compared to 33% (9 of 27 patients) in the 1.0 mg/m^2 dose group. The rate of CR+PR to PS-341 alone was also marginally higher in the 1.3 mg/m^2 group: 38% (10 of the 26 patients) compared with 30% (8 of the 27 patients) in the 1.0 mg/m^2 dose group. The numbers were too small to reach statistical significance.

Conclusions: The recommended dose of VELCADE is 1.3 mg/m^2/dose administered as a bolus intravenous injection twice weekly for two weeks (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12-21). This 3-week period is considered a treatment cycle. Efficacy appears to be marginally better at 1.3 mg/m^2/dose compared with 1.3 mg/m^2/dose, but differences were not statistically significant. Although there is insufficient data on efficacy at the lower (1.0 mg/m^2) dose to recommend the inclusion of this dose in the label, this dose appears to be more tolerable. Information should be provided concerning the tolerability and efficacy of the two doses so providers can make an informed judgement regarding dose selection.

5 Special Populations

5.1. Effects of Gender

Of the 256 patients entered in both phase 2 studies, 44% (112) were female. No differences in response rates were noted for males (26%) compared to females (29%). Males patients had more grade 3 or 4 adverse events compared with female patients (85% and 76%, respectively). However, review of the data revealed no differences in incidence rates of serious adverse events or discontinuations due to adverse events between males and females. However, females were more likely to report musculoskeletal (72% females, 58% males), eye disorders (38% females, 24% males), and fatigue (60% females, 49% males). Males were more likely to experience thrombocytopenia (47% males, 34%, females), and respiratory disorders (61% males, 51% females). No statistically significant differences between males and females in toxicity where found in the 2 phase 2 studies.

5.2. Effects of Age

Among 202 patients in the single arm phase II study (025), 35% were age 65 or older. A higher response rate was observed in patients <65 years of age (32%) as compared to patients ≥65 years (19%), but this response did not reach statistical significance (p=.064). The incidence of grade 3 or 4 AEs increased with patient age from 74% (patients ≤ 50 years) to 80% (51-65 years) to 85% (patients > 65 years). However, there was no apparent difference in the reported incidence of serious events and study discontinuation due to adverse events for those patients between 51 and 65 years and those > 65 years. The incidence of metabolism and nutrition disorders (e.g., anorexia, dehydration), vascular disorders (hypotension), cardiac disorders (tachycardia,

congestive cardiac failure), respiratory disorders (dyspnea) increased with increasing age. Review of the most commonly reported adverse events revealed that anorexia and dehydration, as well as dyspnea NOS had incidence rates that increased with age categories and differed by more than 10%. The reported incidence rate of dyspnea NOS was higher in the 2 older patient groups relative to the younger patients with incidence rates of 8%, 23%, and 28% in patients ≤ 50, 51 to 65, and > 65 years of age, respectively. Older patients were more likely to report constipation (45%) during the study than those patients <50 years of age (26%). Overall, the incidence of diarrhea did not reveal any apparent age relationship. However, the incidence of Grade 3 or 4 diarrhea increased with increasing age group, with 3%, 5%, and 13% of patients ≤50 years, 51 to 65 years, and > 65 years of age, respectively, experiencing at least 1 episode of Grade 3 or 4 diarrhea.

The safety of VELCADE in children has not been studied. Protocol ADVL0015, a phase I study to determine MTD and phase II dose in children (Children's Oncology Group - COG) has enrolled 6 patients to date at a dose level of 1.2 mg/m2 twice-weekly for two weeks each 21 days.

5.3. Effects of Race

Over 80% of the phase II study (025) patients were white. Only 27 black patients and 20 asian/other patients were included in study 025. A marginally higher response rate was observed in Black patients (48%) as compared to White patients (24%) or patients of other races (33%); these differences did not reach statistical significance (p=.064). Overall there were no differences in incidence rates of Grade 3 or 4 adverse events, serious adverse events or discontinuations due to adverse events based on patient race. Two adverse event categories reported differences between racial groups: musculoskeletal and connective tissue disorders, reported in 61% (white) compared to 81% (non-white) of patients, respectively, and psychiatric disorders (50% -white and 32%- non-white, respectively). Review of the most commonly reported adverse events revealed that white patients were more likely to experience fatigue (56%) than non-white patients (45%); diarrhea (50%, 38%) and pyrexia (38%, 25%) were also more frequently reported in white patients compared to non-white patients.

Clinical Review

I. Introduction and Background

1 Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Proposed Trade name: VELCADE™
Proposed generic name (bortezomib)
Drug class: proteasome inhibitor

Proposed indication: VELCADE ™ (bortezomib) for Injection is indicated for the treatment of

The recommended dose of VELCADE is 1.3 mg/m^2/dose administered as a

2 State of Armamentarium for Indication(s)

Myeloma Background

Multiple myeloma (MM) is a malignant plasma cells disorder accounting for about 10% of hematological malignancies. The disease is characterized by the clonal proliferation of plasma cells which produce a monoclonal immunoglobulin heavy and/or light chain (paraprotein, M-protein or M-component). This patient-specific paraprotein is present in the serum and/or urine of all patients except in the 1-2% of patients with non-secretory myeloma. Typical clinical and laboratory features in patients with MM include bone pain (due to lytic lesions or osteoporosis), anemia, renal insufficiency, hypercalcaemia, increased susceptibility to infection and constitutional symptoms resulting in poor performance status. Less common complications include cord compression due to extramedullary plasmacytomas or vertebral collapse, peripheral neuropathy, amyloidosis and hyperviscosity syndrome. MM remains a fatal disease: median overall survival does not exceed 3 years with conventional chemotherapy approaches.

FDA Approved Drugs for the treatment of Multiple Myeloma

Melphalan (Alkeran) for the palliative treatment of MM
Cyclophosphamide (Cytoxan) for the palliative treatment of MM
Carmustine (BCNU) for the palliative treatment of MM
Pamidronate (Aredia) for the treatment of osteolytic lesions of MM
(Zometa) for the treatment of patients with MM

Drugs and combinations used in the treatment of Multiple Myeloma

Corticosteroids (maintenance Rx improves survival)
Combination and high dose chemotherapy
VAD (vincristine adriamycin dexamethasone)
VCMP (Vincristine cytoxan melphalan prednisone)
Thalidomide
Rituximab

Melphalan and prednisone induces a response in about 50–60% of initially-diagnosed MM patients: disappearance of M component by electrophoresis occurs in about 3% of patients. Other approaches have failed to improve upon the results of standard therapy. A meta-analysis of 4,930 patients from 20 trials was performed to see if there was a correlation of increased intensive therapy, response rates, and survival:[2] Pooliing the results of all 20 trials together, response rates were significantly higher with CCT than with MP (60.0% v 53.2%; $P < .00001$, two-tailed). However, there was no evidence of any difference in mortality between CCT and MP, with a non significant 1.5% reduction in death rate in favor of CCT ($P = .6$, two-tailed). Blade, *et al*, reported on the long-term results of two randomized Spanish trials which included 914 patients with myeloma treated with either melphalan and prednisone or more intensive combination chemotherapy. In these trials, the response rate, as defined as a 50% reduction in M protein amount, significantly correlated with the regimen intensity. However, no significant differences in response duration and survival were found. Increased response rates do not seem to be correlated with improved survival, in the initial treatment of multiple myeloma.[3]

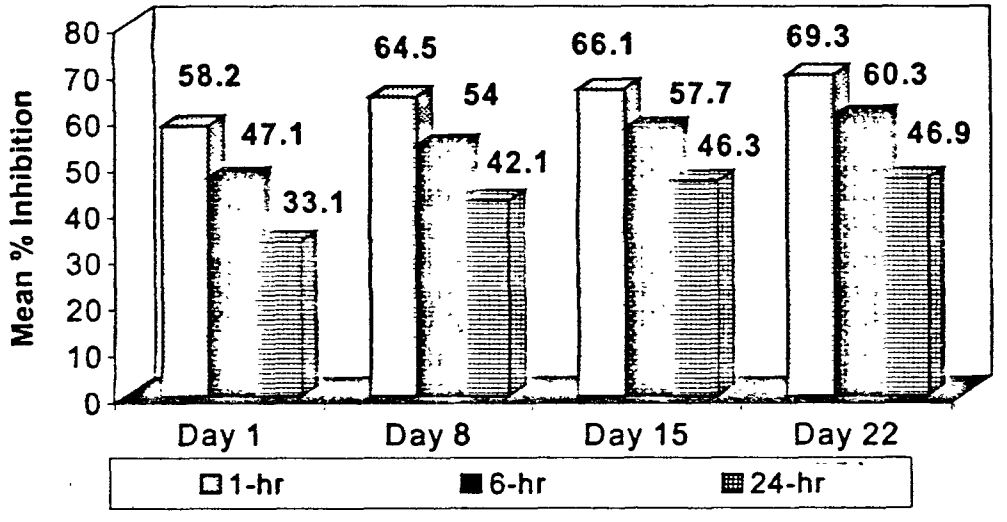
High-dose chemotherapy followed by autologous stem cell transplantation however does appear to have a survival benefit over conventional treatment and is currently the accepted mode of treatment for symptomatic MM in eligible patients. The percentage of remissions has increased ten-fold from 1–3% with conventional dose therapy up to almost 30 % with high dose therapy (Table 2). Remission duration has been prolonged by at least 10 months from a median duration of about 18 to 30 months. Overall survival has improved from about 30 to 60 months. Despite these therapeutic improvements the disease tends to recur in all patients: molecular evaluations of minimal residual disease are able to detect neoplastic myeloma cells in virtually all patients after a single or a double autologous transplant.[4] The development of resistance to chemotherapy determines disease progression, which is the major cause of death. Allogeneic transplantation is associated with higher complete remission rates, but at the cost of high therapy-related mortality. A cure in MM appears to be achievable only by allogeneic transplantation: about 50% of transplanted patients become molecularly negative and remain in complete remission (CR) for several years.[5] However, few patients can tolerate allogeneic procedures, and the disease inevitably recurs after standard dose therapy, creating a population of relapsed patients who have been exposed to multiple cycles of chemotherapy.

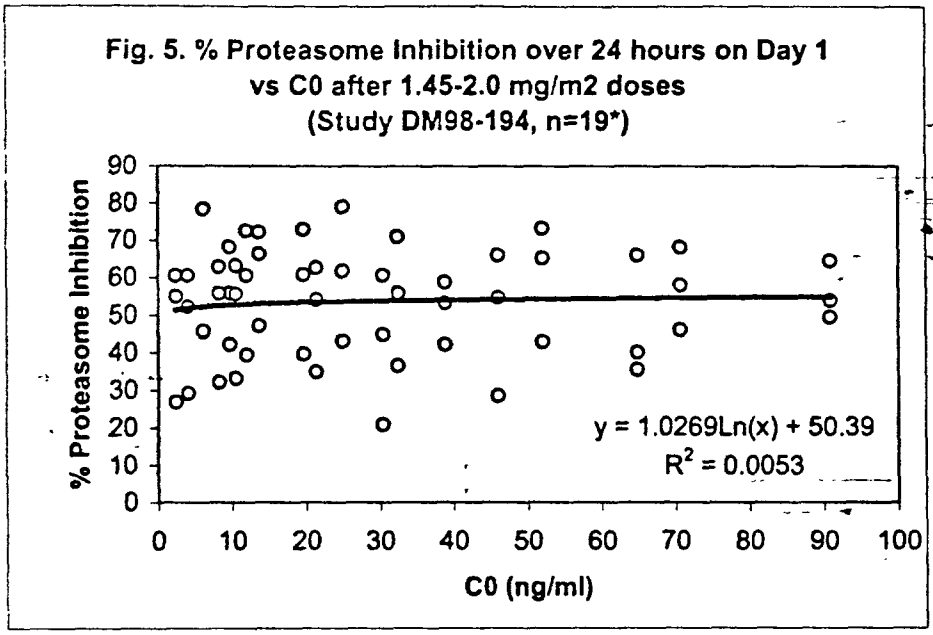
Many drugs have been shown to elicit a clinical response in patients with relapsed MM (Table 2):

removed such analyses by Amendment 1 to Protocol LCCC 9834 on September 13, 1999. Therefore, no samples for pharmacokinetic analyses were collected in this study.

The results of these studies demonstrate that mean % proteasome inhibition activity is consistently higher at 1 hr than at 6 hr or 24 hr after dosing at any day and higher on last day of dosing than the first day at 1, 6, or 24 hr after dosing (Fig. 4). However, the time at which maximum inhibition occurs is not known. At doses of 1.45-2.0 mg/m^2, a poor correlation is noted between the % proteasome inhibition at 1, 6, and 24 hr after dosing on Day 1 and estimated maximum plasma concentration (C_0) (r=0.07), suggesting fact that at these doses, the % proteasome inhibition may have reached a plateau (Fig. 5). C_0 was estimated as the zero time intercept of the extrapolated initial distribution phase of the log-linear plasma concentration/time plot. The relationship between % proteasome inhibition and dose (Fig. 6) indicate that the optimum PS-341 dose may be between 1.0 mg/m^2 and 1.3 mg/m^2. The results also demonstrate that there is no difference in the mean % inhibition and whether PS-341 was administered once weekly, twice weekly for two weeks, or twice weekly for four weeks (Fig. 7). In overall, the variability in % inhibition is low (< 20%) (Tables 2-4).

Fig. 4. Mean % proteasome Inhibition *vs* Days (Study DM98-194)





(*2 outliers and 3 patients with no inhibition data were excluded from the database)

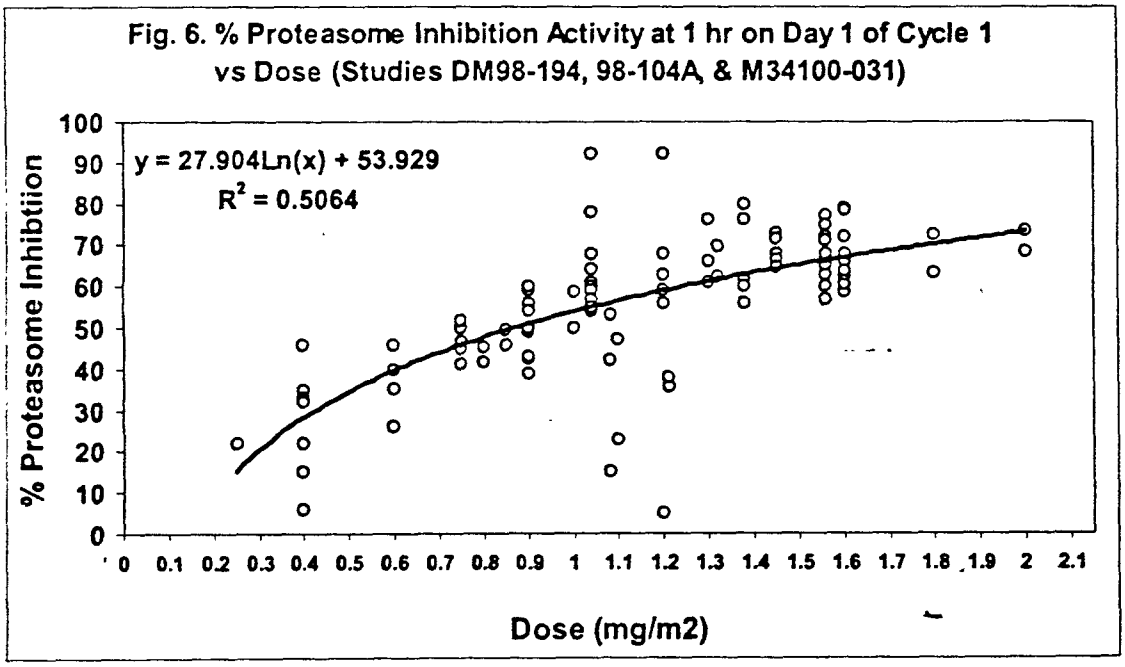


Fig. 7. Mean % proteasome Inhibition at 1 hr vs Schedules
(Studies DM98-194, 98-104A, LCCC9834/00-31)

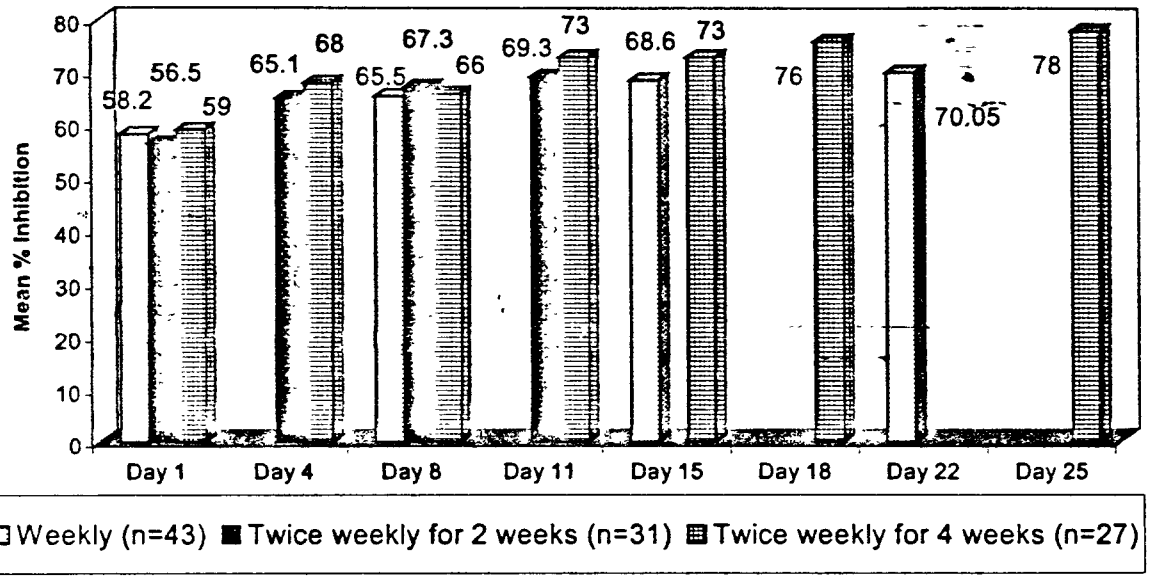


Table 2. Mean (±SD) % inhibition of 26S proteasome activity compared to pre-treatment baseline (Study DM98-194):

Dose (mg/m^2)	Cycle 1 (n=45)											
	Day 1			Day 8			Day 15			Day 22		
	1-hr	6-hr	24-hr	1-hr	6-hr	24-hr	1-hr	6-hr	24 hr	1-hr	6-hr	24-hr
0.25 (n=1)	22	NC	NC	48.2	43.1	46.8	52.6	55.4	41.5	44.3	48.2	51.8
0.4 (n=2)	NC, NC	31.6, NC	41.05, 16.9	24, NC	35.7, NC	45.6, 23.3	34.8, 11.6	33.9, 10.6	24.7, NC	60.6, 39.7	56.4, 27.4	56, 16.1
0.6 (n=2)	35.3, NC	21.7, NC	NC, NC	35.7, 26.2	36.6, 4.9	32.4, NC	38.8, NC	44.2, NC	NC, 54.4	47.5, 67.3	23.01, 67.1	23.9, 59.5
0.75 (n=2)	41.2, 50.2	23.9 NC	15.7, 27	51.5, 62.5	48.35, 56.3	40.9, 49.8	45.9, 61.1	47.6, 41.4	37.3, 43.8	57.8, 62.3	53.5, 59.5	44.1, 48.7
0.8 (n=3)	41.8 (2.5)	38.9 (5.3)	28.1 (4.9)	51.8 (2.1)	44.1 (3.2)	34.9 (13.5)	58.2 (5.2)	53.1 (7.1)	40.25 (13.6)	65.5 (4.3)	61.2 (1.5)	50.9 (7.5)
0.85 (n=2)	46.1, 49.5	34.3, 30.3	25.4, 27.7	55.2, 77.8	69.5, 35.4	59.6, 20.8	64.3, 55.7	52.8, 62.2	36, 59.6	75.8, 49.7	71.6, 42.2	61.2, 32.6
0.90 (n=2)	42.6, 49.2	31.4, 35.9	15.9, 20.6	54.2, 48.5	45.3, 42.9	26.6, 26.5	50.2, 53.8	44.8, 45.5	30.1, 26.4	48.1, 48.8	39.3, 32.4	31.6, 30.4
1.0 (n=2)	50, NC,	46.7, NC,	21.4, NC,	44.3, 58.7	26.1, 42.8	8.9, 26.7	57.5, 69.6	47.3, 51.9	39.5, 31.5	61.4, 65.8	54.8, 51.7.	43.9, 31.2
1.1 (n=2)	47.05, NC	42.7, NC	34.3, 23.1	53.7, 49.1	51.4, NC	32.5, NC	59.9, 64.2	53.9, 51.2	52.8, 39.8	65.7, 74.6	54.1, 50.9	10.8, 42.7
1.21 (n=2)	35.9, 38.2	NC, NC	NC, NC	65.9, 58.9	32.1, 40.9	27.7, 33.2	44.1, 66.5	34.4, 57.4	3.3, 45.1	NC, NC	NC, NC	NC, NC
1.32 (n=2)	69.5, 62.5	NC, 40.5	37.8, 21.3	78.1, 79.8	68.5, 63.7	56.5, 40.6	83.7, 83.7	79.2, 74.9	58.2, 52.1	78.2, 76.4	66.1, 68.4	65.2, 62.9
1.45 (n=6)	68.0 (3.5)	52.3 (6.8)	43.6 (6.3)	78.0 (2.5)	67.6 (4.1)	51.0 (4.5)	72.7 (10.3)	63.4 (5.6)	50.5 (11.7)	78.2 (2.9)	69.6 (3.8)	54.8 (5.9)
1.6 (n=13)	66.5 (6.7)	53.1 (7.2)	36.2 (8.1)	73.8 (6.6)	62.2 (10.3)	46.5 (11.8)	76.9 (6.1)	66.1 (8.5)	50.8 (9.1)	77.0 (4.5)	66.7 (9.3)	50.2 (9.1)
1.8 (n=2)	72.5, 63.1	60.5, 55.6	39.4, 33.1	72.2, 45.9	69.7, 38.9	62.6, 18.2	87.1, 53.8	80.4, 32.8	64.5, NC	81.4, 73.3	78.6, 61.4	61.3, 45.5
2.0 (n=2)	73.3, 68.2	65.3, 58.1	43.1, 46.2	80.3, 81.7	67.8, 50.3	55.6, 65.4	86.5, 80.8	71.9, 72.2	66.5, 52.1	87.7, 78.3	80.8, 69.02	55.6, 50.4
Total (n=45)	58.2 (13.7)	47.1 (11.9)	33.1 (9.9)	64.5 (15 7)	54.0 (15 7)	42.1 (14.2)	66.1 (16.5)	57.7 (14.7)	46.3 (13.3)	69.3 (12.)	60.3 (13.8)	46.9 (13.9)

Table 3. Mean (±SD) % inhibition of 26S proteasome activity compared to pre-treatment baseline (Study 98-104A):

Dose (mg/m^2)	Cycle 1 (n=31)							
	Day 1		Day 4		Day 8		Day 11	
	1-hr	24-hour	1-hr	24-hr	1-hr	24-hr	1-hr	24-hr
0.6 (n=4)	44.5 (3.0)	6.7 (7.0)	51 (5.0)	NC	43 (6.0)	19 (13)	59 (6.0)	NC
0.75 (n=3)	48 (4.0)	22 (12.0)	60 (7.0)	NC	60 (6.0)	31 (9.0)	60 (5.0)	NC
0.9 (n=6)	51.5 (8.0)	21 (9.0)	64 (10)	NC	68 (5.0)	46 (18)	69 (9.0)	NC
1.08 (n=3)	37 (20)	12 (9.0)	59 (11)	NC	67 (9.0)	49 (2.0)	76 (3.0)	NC
1.3 (n=3)	68 (8.0)	23 (9.0)	65 (23)	NC	56 (21)	15 (35)	59.5 (6.0)	NC
1.56 (n=12)	68 (7.0)	34 (6.0)	74 (5.0)	NC	79 (4.0)	51 (7.0)	77.5 (6.0)	NC

NC (Not Calculated)

Table 4. Mean (±SD) % inhibition of 26S proteasome activity compared to pre-treatment baseline (Study LCCC9834/00-31):

Dose (mg/m^2)	Cycle 1 (n=27)											
	Day 1			Day 4			Day 8			Day 11		
	1-hr	6-hr	24-hr	1-hr	6-hr	24-hr	1-hr	6-hr	24-hr	1-hr	6-hr	24-hr
0.4 (n=3)	26 (10)	17 (5.8)	5 (14)	36 (1.2)	24 (13)	10 (9.7)	28 (13)	22 (2.7)	17 (8.7)	22 (13)	30 (6.7)	28 (11)
1.04 (n=12)	62 (12)	43 (9.6)	25 (9.4)	69 (11)	60 (4.6)	32 (13)	71 (12)	59 (6.9)	43 (15)	77 (3.7)	64 (10)	48 (8.9)
1.2 (n=7)	66 (14)	52 (19.8	29 (13)	73 (6.2)	59 (5.9)	39 (14)	72 (14)	67 (8.6)	51 (12)	83 (2.9)	65 (5.0)	51 (9.3)
1.38 (n=5)	65 (7.9)	49 (9.2)	37 (4.3)	77 (3.1)	60 (8.6)	41 (10)	75 (19)	69 (5.2)	53 (6.3)	87 (7.2)	64 (8.3)	41 (15)
Dose (mg/m^2)	Cycle 1 (n=27)											
	Day 15			Day 18			Day 22			Day 25		
	1-hr	6-hr	24-hr	1-hr	6-hr	24-hr	1-hr	6-hr	24-hr	1-hr	6-hr	24-hr
0.4 (n=3)	35 (2.0)	26 (8.3)	13 (10)	57 (44)	20 (11)	17 (0.9)	47 (2.2)	45 (9.3)	39 (0)	48 (10)	44 (13)	27 (13)
1.04 (n=12)	73 (9.5)	62 (13)	52 (4.7)	75 (10)	61 (11)	52 (10)	80 (8.6)	71 (15)	57 (6.6)	81 (6.8)	71 (5.2)	57 (6.6)
1.2 (n=7)	82 (7.4)	59 (21)	48 (14)	82 (3.8)	72 (7.7)	54 (15)	75 (10)	67 (5.2)	53 (3.9)	85 (1.3)	78 (2.7)	49 (0)
1.38 (n=5)	79 (9.1)	75 (4.2)	55 (2.2)	90 (4.2)	75 (0.7)	57 (5.1)	91 (6.9)	80 (8.5)	53 (10)	87 (2.6)	80 (9.7)	NC

The % proteasome inhibition activity was also determined during the Phase 2 Studies *M34100-024 and M34100-025.*

In *Study M34100-024*, the 26S proteasome inhibition activity in whole blood was determined in blood samples collected before and at 1 hr after PS-341 dosing on Days 1 and 11 of each of Cycle 1 and Cycle 7 after the 1.0 mg/m^2 and 1.3 mg/m^2 doses (Table 5).

Table 5. Mean (±SD) % 26S proteasome inhibition activity compared to pre-treatment baseline (*Study M34100-024*):

Dose	Cycle 1				Cycle 7			
	Day 1		Day 11		Day 1		Day 11	
	Pre-dose	1-hour	Pre-dose	1-hour	Pre-dose	1-hour	Pre-dose	1-hour
1.0 (mg/m^2)	0.0	57 (14.5)	21 (55.2)	71 (25.1)	12.7 (26.4)	57 (27.8)	21 (36.8)	59 (24.8)
n	14	14	14	14	7	5	9	8
1.3 (mg/m^2)	0.0	70.5 (14.7)	23 (22)	79 (80.4)	-1.7 (13.7)	55 (2.04)	15.3, 34.3	24, 75.1
n	11	11	10	7	4	3	2	2

From these data, the mean % 26S proteasome inhibition activity at 1 hr increases with the increase in dose from 1.0 mg/m^2 to 1.3 mg/m^2 on Day 1 of Cycle 1 (57% vs 70.5%). However, on Day 1 of Cycle 7, the mean % inhibition at 1 hr remains the same (57% *vs* 55%, respectively) as the dose increased from 1.0 mg/m^2 to 1.3 mg/m^2. At the 1.0 mg/m^2 dose, the 1-hr mean % inhibition on Day 1 of Cycle 1 is the same at the corresponding value of Cycle 7 (57%); however, on Day 11, it decreases from 71% to 59%. At the 1.3 mg/m^2 dose, the 1-hour mean % inhibition on Day 1 Cycle 1 is higher than the corresponding value of Cycle 7 (70.5% *vs* 55%). The Co-administration of dexamethasone may slightly increase the inhibition of 26S proteasome activity by PS-341. In patients who were administered PS-341 in combination with dexamethasone, the mean (SD) % inhibition of 26S proteasome activity at 1 hr after dosing in Cycle 1 is 65% (24.6%) after the 1.0 mg/m^2 dose (n=6) and 73% (13.9%) after the 1.3 mg/m^2 dose (n=4).

In *Study M34100-025*, the 26S proteasome inhibition activity in whole blood was determined from blood samples collected before and at 1 hr after dosing on Days 1 and 11 of each of Cycle 1 and Cycle 7 (Table 6).

Table 6. Mean (±SD) % inhibition of 26S proteasome activity compared to pre-treatment baseline (pre-dose on Day 1, Cycle 1):

Dose	Cycle 1				Cycle 7			
	Day 1		Day 11		Day 1		Day 11	
	Pre-dose	1-hour	Pre-dose	1-hour	Pre-dose	1-hour	Pre-dose	1-hour
1.3 (mg/m^2)	0.0	61 (15.5)	31 (24.8)	76 (15.1)	19 (29.9)	38 (19.2)	30 (22.1)	72.5 (11.9)
n	141	141	115	108	41	38	33	31

The mean % proteasome inhibition activity at 1 hr on Day 1 of Cycle 1 is about 1.6-fold higher than that on Day 1 of Cycle 7 (61% *vs* 38%). In Day 11, it was similar between the two cycles (76% *vs* 72.5%). Co-administration of dexamethasone may slightly increase the inhibition of 26S proteasome activity by PS-341. In patients who were administered PS-341 in combination with dexamethasone (n=22), the mean (±SD) % inhibition of 26S proteasome activity at 1 hr after dosing in Cycle 1 is 69% (23.5%).

Are the active moieties in serum appropriately identified and measured to assess pharmacokinetic parameters and exposure/response relationships?

In vitro studies with human liver microsomes and human cDNA-expressed CYP isozymes indicate that PS-341 is extensively metabolized to eight major metabolites (M1-M8) by CYP 1A2, 2C9, 2C19, 2D6, and 3A4 enzymes (Table 7 and Fig. 8) ***(Report RPT-00033)***. The major proposed metabolic pathway for PS-341 is deboronation to form metabolites M1 and M2. Deboronated metabolites could be also formed via non-enzymatic (chemical) degradation (metabolites A and B). The deboronated metabolites (M1 and M2 and A and B) subsequently undergo hydroxylation (minor pathway) to form a number of hydroxylated metabolites.

Table 7 PS-341 metabolites as percent of total metabolism

In vitro System*		PS-341 (25 μM)					
		M1/M2 (A/B)	M3 (C)	M4 (D)	M5/M6	M7	M8
Microsomes (1 mg/ml protein)		43%	11%	4%	25%	10%	7%
CYP1A2	(25 pmol/ml)	85%	11%	0%	<1%	4%	0%
CYP2C9	(25 pmol/ml)	81%	10%	0%	4%	5%	0%
CYP2C19	(25 pmol/ml)	58%	8%	0%	10%	24%	0%
CYP2D6	(25 pmol/ml)	86%	6%	0%	1%	7%	0%
CYP3A4	(25 pmol/ml)	76%	13%	0%	4%	6%	0%

*(in Triplicates)

Fig. 8. Proposed PS-341 Metabolic Pathways (Applicant's)

The Applicant has not evaluated the activity of PS-341 metabolites, but it is believed that the deboronated and hydroxylated metabolites are inactive as 26S proteasome inhibitors (Nonclinical Summary).

In vitro studies with human cDNA-expressed CYP isozymes (1A2, 2C9, 2C19, 2D6, or 3A4) indicate that PS-341 is primary a substrate of 3A4 ***(Report RPT-00011)***. Approximately 60% of PS-341 was metabolized by 3A4 in 60 minutes (Table 8). CYP 2D6, 2C19, 1A2, and 2C9, metabolized 50%, 33%, 23%, 21% and 50% of PS-341 in 60 minutes, respectively.

Table 8. Mean (SD) % of PS-341 remaining by recombinant human CYP isozymes

	% Substrate Remaining at 60 Minutes (n=3)				
Compounds (Concentration)	1A2	2C9	2C19	2D6	3A4
PS-341 (200 µM)	76.9± 3.1	79.6± 5.8	66.7 ± 3.7	49.5± 7.1	38.7±1.5
Ethoxyresorufin (20 µM)	5.05± 0.61				
Diclofenac (20 µM)		4.07±1.55			
Mephenytoin (20 µM)			33.1± 0.69		
Dextromethorphan (20 µM)				2.03± 0.16	
Midazolam (20 µM)					2.04± 0.17

1. Incubations were conducted using 25 pmols of recombinant human CYP P450 isozymes and an NADPH-generating system in 0.1M tris buffer, pH 7.4 for 0, 15, 30, 45, and 60 minutes at 37°C.
2. Ethoxyresorufin, diclofenac, mephenytoin, dextromethorphan and midazolam were used as positive controls.

Plasma samples collected from 8 patients with advanced malignancies ***(Study DM198-194)*** 10 min and 30 min after dosing at doses of 1.6 mg/m^2 (n=3) and 2.0 mg/m^2 (n=5) on day 1, cycle 1 were pooled and analyzed for PS-341 as well as its identified metabolites. The data indicate that plasma levels of metabolites are low compared to the parent drug (Table 9). Unchanged PS-341 is the only drug-related entity measured in clinical pharmacology studies and used to assess the pharmacokinetic parameters and exposure/ response relationships.

Table 9. PS-341 metabolites levels identified in human plasma– Pooled from 8 patients (Study DM98-194)

Metabolite	Plasma concentration (ng/ml) at 10 min after dosing (n=8 patients)	Ratio PS-341/M	Plasma concentration (ng/ml) at 30 min after dosing (n=8 patients)	Ratio PS-341/M
PS-341	29.7		9.63	
M1	1.9	15.6	1.2	8.0
M2	3.4	8.7	3.7	2.6
M3	0.63	47	0.47	20.5
M4	1.5	19.8	1.7	5.7
M5	0.53	56	0.58	16.6
M6	0.74	40	1.0	9.6
M7	0.19	156	0.18	53.5
M8	0.11	270	0.17	56
M23	0.089	333	0.073	132
M24	0.064	464	0.055	175
M29	0.11	270	0.17	56
M30	0.43	69	0.48	20

Excretion

No excretion data for PS-341 are available in humans. Animal data indicate that PS-341 is eliminated through both renal and hepatic routes (Nonclinical Summary). In intact rats, 38.6% of the administrated radioactivity is excreted in the feces, 21% in the urine, and 6.1% in expired air. In bile duct cannulated rats, 35.1% of the administered radioactivity is recovered in bile, 16.2% in urine, 7.75 % in feces, and 1.2% in expired air.

What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

- **Is the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?**

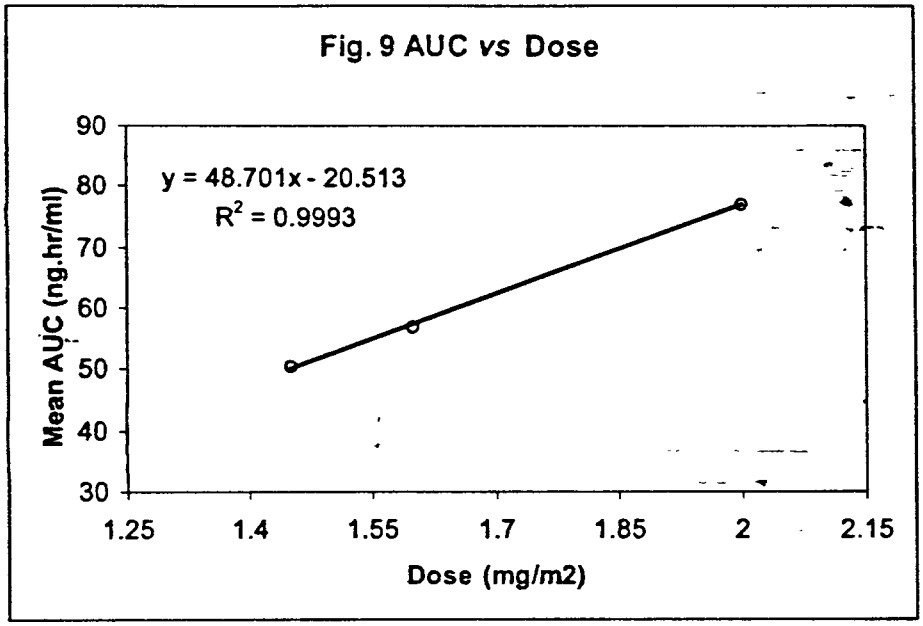
The Applicant used the maximum tolerated dose (MTD) and dose-limited toxicity (DLT) determined in the Phase 1, dose-escalation studies (DM98-194, 98-104A, LCCC9834/00-31) to guide the selection of PS-341 dose and dosing schedule that was used in pivotal Phase 2 Study M34100-025 in patients with multiple myeloma. One-hundred twenty-three patients were evaluated in the Phase 1 Studies DM98-194, 98-104A, LCCC9834/00-31 at doses ranging from 0.13 mg/m^2 to 2.0 mg/m^2 and at three different schedules: weekly for four weeks, twice weekly for two weeks, and twice weekly for four weeks (see Applicant's Table below):

Protocol Number Patient Population	PS-341 Dose (mg/m^2)	Dosing Regimen	MTD (mg/m^2)	DLT
Study DM98-194: Solid tumor N=53	0.13 –2.0	1x per week for 4 weeks (Days 1, 8, 15, and 22)	1.6	Diarrhea, hypotension (including Orthostatic hypotension), tachycardia NOS, vision abnormal NOS, and syncope
Study 98-104A: Solid tumor N=43	0.13 –1.56	2x per week for 2 weeks (Days 1, 4, 8, and 11)	1.3	Diarrhea, peripheral sensory Neuropathy
Study LCCC 9834 / 00-31: Hematologic malignancies N=27	0.4 –1.38	2x per week for 4 weeks (Days 1, 4, 8, 11, 15, 18, 22, and 25)	1.04	Hyponatremia, hypokalemia, malaise

These studies, two conducted in patients with solid tumors (Studies DM98-194, 98-104A) and one in patients with hematological malignancies (Study LCCC9834/00-31), demonstrated an MTD of PS-341 ranging from 1.04 mg/m^2 to 1.6 mg/m^2 depending on dosing schedule. These studies supported the selection of the twice-weekly schedule at 1.3 mg/m^2 as the most appropriate dose for phase 2 evaluation in multiple myeloma.

- ***Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?***

PS-341 exhibits linear kinetics in cancer patients over the IV bolus doses of 1.45 mg/m^2 (n=4), 1.6 mg/m^2 (n=13), and 2.0 mg/m^2 (n=5) ***(DM98-194)***. Fig. 9 graphically compares mean area under plasma curve (AUC) values versus dose administered.

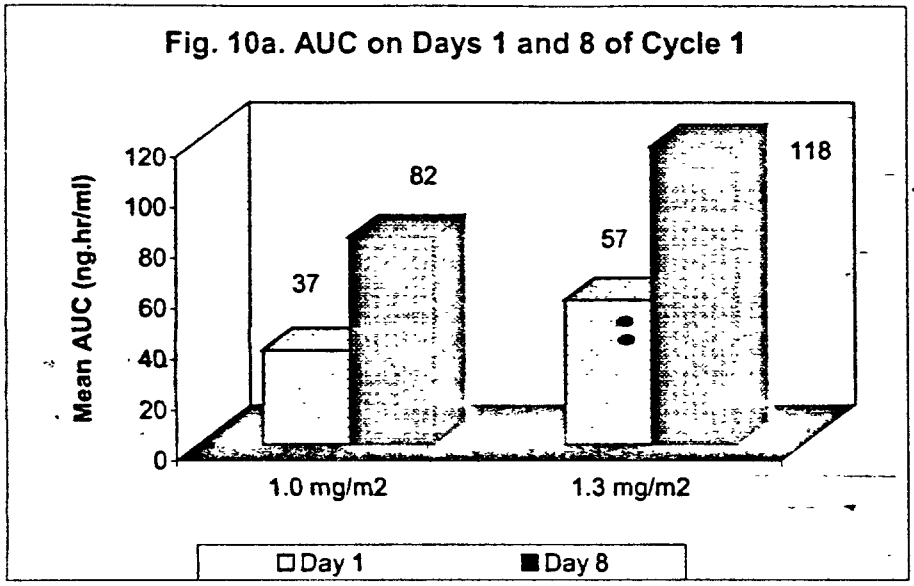


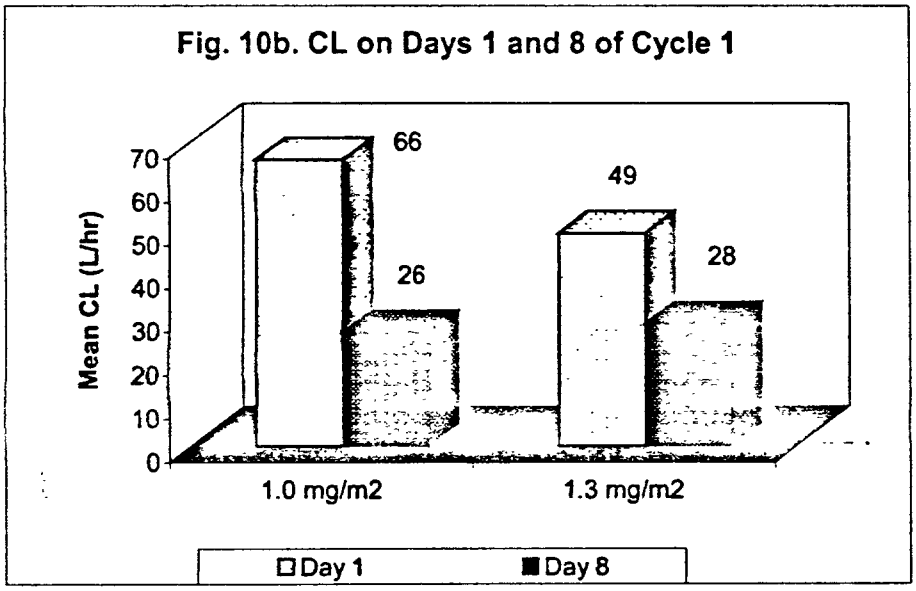
Mean PS-341 AUC increased in proportional to the increase of dose from 1.45 to 2.0 mg/m^2 (r=0.999).

The binding of PS-341 to human plasma proteins was linear over the concentration range of 1.0-1000 ng/ml and averaged 83 ± 3% (Report 6837-101).

- ***How do PK parameters change with time following chronic dosing?***

Interim PK data from the ongoing Phase 2 study ***(Study M34100-027)*** reveal that exposure to PS-341 when given in combination with gemcitabine is higher on Day 8 than on Day 1 of Cycle 1 (Fig. 10 a&b). AUC increased 2.2-fold and its CL decreased by 60% on Day 8 compared to Day 1 at the 1.0 mg/m^2 PS-341 dose; the corresponding values at the 1.3 mg/m^2 PS-341 dose were 2.1-fold and 40%, respectively. This indicates that PS-341 may accumulate upon twice a day administration in the same cycle and this accumulation may contribute to the incidence of adverse events. However, we can not rule out whether this accumulation is due to time-dependent kinetics or due to the effect of gemcitabine on exposure to PS-341. As PS-341 is to be administered to MM patients up to eight cycles; accumulation of PS-341 as a monotherapy during a specific cycle and from cycle to cycle should be investigated (see Phase 4 Commitments).

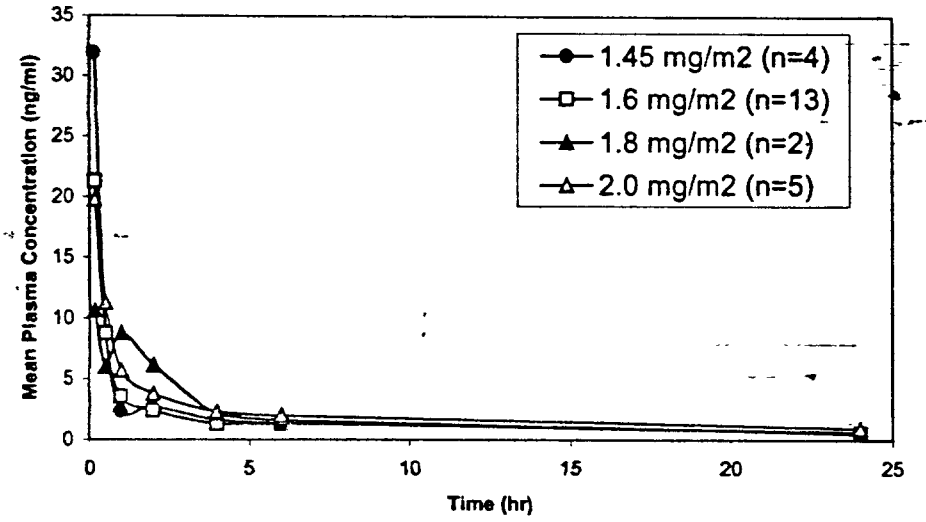




How does the PK of ZD1839 in healthy volunteers compare to that in patients? What is the inter-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

PS-341 is a cytotoxic agent and therefore was not administered to healthy volunteers. Limited PK data are available in patients with multiple myeloma (MM) for PS-341 as a monotherapy at the proposed dose of 1.3 mg/m^2 twice weekly for two weeks.

Fig. 11. Mean PS-341 plasma concentration/time profiles following bolus IV doses (Study DM98-194)



Plasma concentration/time profiles decline biexponentially with a mean elimination half-life ($t_{½}$) ranging from 8 to 15 hours at PS-341 doses of 1.45-2.0 mg/m^2. Mean total body clearance (CL) at these doses ranges from 64 to 112 L/hr; and it is lower than hepatic blood flow rate (Q_H=90 L/hr), indicating that PS-341 has a moderate clearance. PS-341 is widely distributed into tissue with a mean steady state volume of distribution (V_{ss}) value of 416-979 L at PS-341 doses of 1.45-2.0 mg/m^2; this greatly exceeds the volume of total body water (42 L). The inter-subject variability in PK parameters is considerably high, 33% to 180%).

- Interim PK data were obtained in an ongoing Phase 2 study of PS-341 in combination with gemcitabine (***Study M34100-027***).

To date, 21 patients with advanced solid tumors received the PS-341/gemcitabine combination at doses of 1.0/500 (n=3), 1.0/800 (n=2), and 1.0/1000 mg/m^2 (n=12) and 1.3/800 mg/m^2 (n=5). Blood samples were collected pre-dose and at 5, 15, and 30 min and 1, 1.5, 2.5, 4.5, 6.5, and 24 hr after bolus IV administration of PS-341 on Days 1 and 2 and on Days 8 and 9 of Cycle 1 (Dose 1 and 3). PS-341 levels were measured in plasma samples using a LC/MS/MS assay method. Because this was an interim study report, no assay validation has been submitted. Table 11 summarizes the mean PK parameters of PS-341 following administration to 21 cancer patients during Cycle 1.

Table 11. Mean±SD (%CV) PK parameters of PS-341 in combination with gemcitabine in 21cancer patients during Cycle 1(Study M34100-027)

Parameter	PS-341 Doses			
	1.0 mg/m^2 (n=17)		1.3 mg/m^2 (n=5)	
Days of Cycle 1	Day 1	Day 8	Day 1	Day 8
C_0 (ng/ml)	158±130 (82%)	126±87 (69%)	173±218 (126%)	85±29 (34%)
AUC (ng hr/ml)	37±18.3 (49%)	82±26 (32%)	57±20 (33%)	118±47.8 (40%)
t½ (hr)	5.5±4.5 (82%)	19.7±11.6 (59%)	9.1±6.03 (65%)	16.6±7.9 (47%)
CL (L/hr)	66±33 (50%)	26±8.8 (34%)	49±13 (26%)	28±22 (78%)
V_z (L)	441±230 (52%)	663±338 (51%)	614±395 (64%)	497±75 (15%)

In the above table, although the PK parameters for PS-341 were determined at the proposed dose of 1.3 mg/m^2, these data will not be considered for labeling for the following reasons:

- The data are confounded by the presence of gemcitabine (its effect on the PK of PS-341 is not known),
- The sample size is small (n=5), and
- These data are interim data and no assay validation was submitted.

C. Intrinsic Factors and Special Populations

What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics? Are dosage adjustments recommended for any of these subgroups?

a) *Age, Gender, and Race:* The Applicant has not performed any analysis to evaluate the effects of age, gender, race, or other demographics on the PK of PS-341. The ongoing population PK analysis of the data from the phase 3 study in multiple myeloma patients may assess these effects ***(Study M34101-039)***.

b) *Hepatic impairment:* The Applicant has not conducted a formal PK study to assess the effect of hepatic impairment on the PK of PS-341 (see Phase 4 Commitments). No specific dosing recommendations is included in the label for this special population. As PS-341 is partially eliminated by the liver, the label will include a precaution for the use of VELCADE in patients with hepatic impairment.

c) *Renal impairment:* The Applicant has not conducted a formal PK study to assess the effect of in renal impairment on the PK of PS-341 (see Phase 4 Commitments). The pivotal Phase 2 Study ***M34100-025*** included 202 patients with MM and varying degrees of renal impairment; CLcr values ranged from 13.8 to 220 ml/min. There were 74 patients with normal kidney function, 82 with mild renal impairment, 29 with moderate renal impairment, and 15 with severe renal impairment; one patient had a missed CLcr value. Dosing reductions were made from 1.3 mg/m^2 to 1.0 mg/m^2 and from 1.0 mg/m^2 to 0.7 mg/m^2 twice weekly in some patients to avoid toxicities. For patients who had CLcr

values <30 ml/minute, PS-341 dose was modified based on proteasome inhibition data collected at 1 hour post-dose. The level of 26S proteasome activity inhibition was to be >65% and <80%. If inhibition of 26S proteasome activity was 65% or lower or 80% or higher, then the PS-341 dose was to be modified accordingly. During this study (***M34100-025***), plasma PS-341 levels were determined up to two hours after dosing in eight patients. One of the eight patients had a moderate renal impairment (creatinine clearance (CLcr=31.1 ml/min), five had mild renal impairment (CLcr=62.4-79.2 ml/min), and two had normal renal function (CLcr=112 and 169 ml/min). Correlations were explored between CLcr and AUC_{0-2} between CLcr and % proteasome inhibition activity at 1 hr after dosing, and between C_0 and % proteasome inhibition activity at 1 hr after dosing. Results are shown below:

Table 12. PK parameters and % percent 26S proteasome inhibition activity in MM patients following a 1.3 mg/m^2 PS-341 bolus IV dose (Day 1, Cycle 1):

Patient's ID	CLcr (ml/min)	C_0 (ng/ml)	AUC_{0-2} (ng.hr/ml)	% Inhibition 1 hr after dosing (Day1/Cycle 1)
8			46.5	65.8
9			20	62.3
10			32	61.5
11			38.7	58.2
12			79.5	64.8
13			15.0	52.5
14			11.9	34.6
15			40.3	69.9
Mean (SD)			35.5 (21.8)	58.7 (11.04)

*NC (not calculated)

After 1.3 mg/m^2 PS341 dose, the median (range) estimated C_0 determined in seven patients is [redacted] ng/ml. In one patient with a CLcr value of 169 ml/ml with an observed concentration value of 42.8 ng/ml at 2 min after dosing was obtained. There is a trend for AUC_{0-2} and % proteasome inhibition activity to increase at 1 hr as CLcr decreased ([redacted] and [redacted] respectively) (Figures 12 and 13, respectively). The % proteasome inhibition activity at 1 hr tends to increase as C_0 increased (r=0.455) (Figure 14). However, because of the limited data per renal group, no definitive conclusion could be drawn regarding the effect of renal impairment on the PK of PS-341. However, based on the above limited and inconclusive PK data, specific dosing recommendations could not be made in the label for this special population. As PS-341 is partially eliminated by the kidneys, the label will include a precaution for the use of VELCADE in patients with creatinine clearance values < 13 ml/ min and patients on hemodialysis).

Fig. 12. AUC0-2 *vs* CLcr

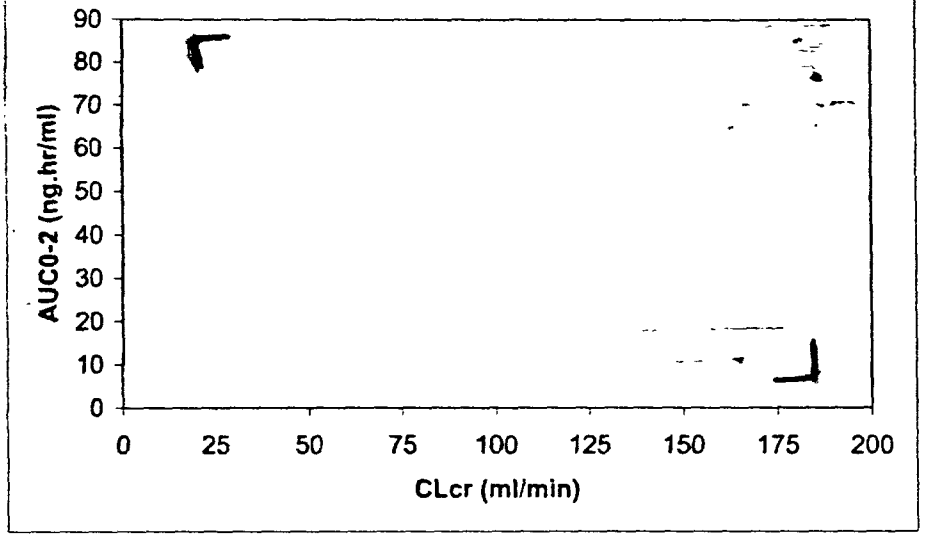
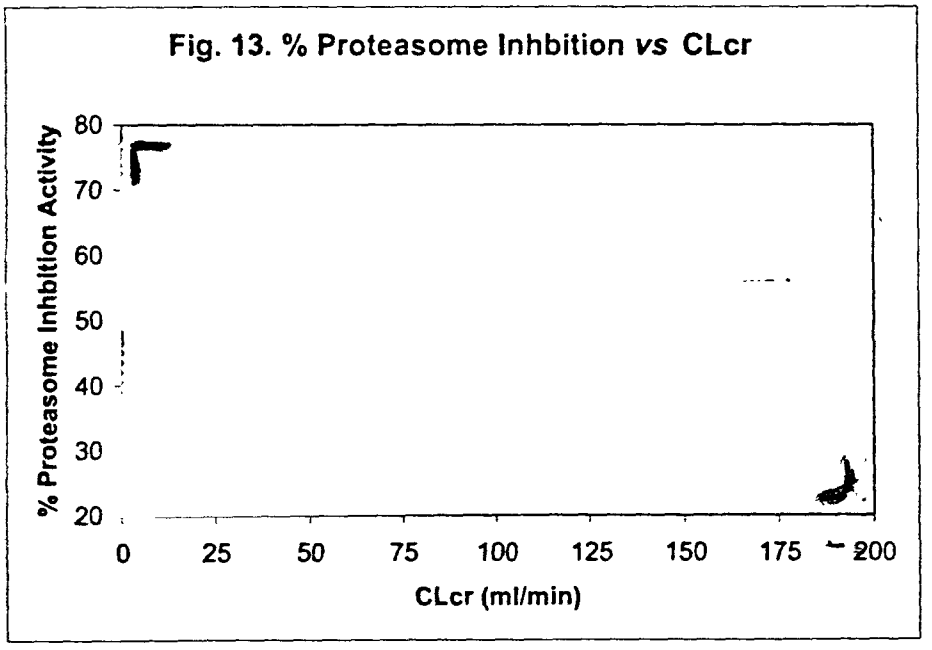
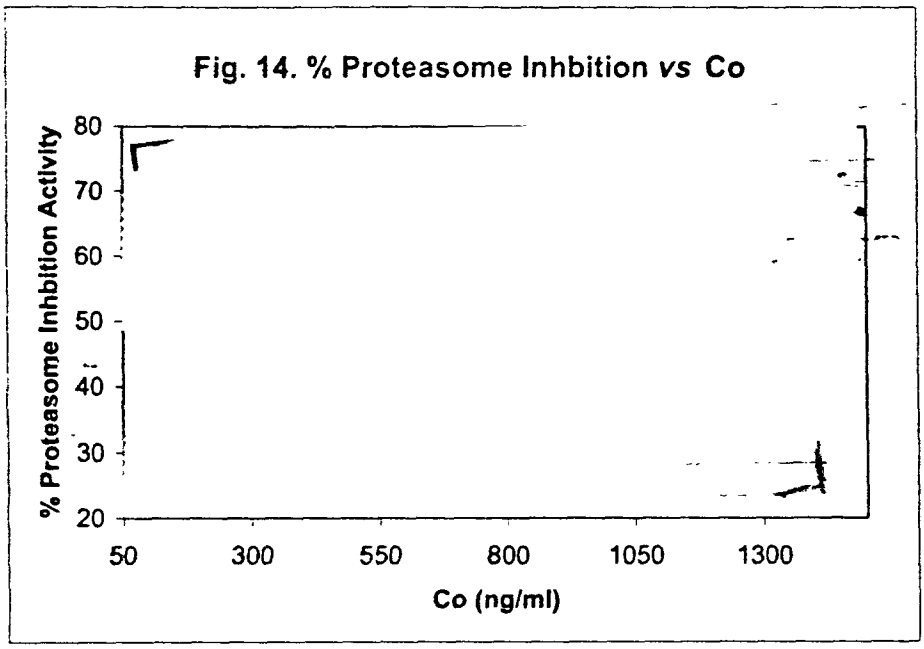


Fig. 13. % Proteasome Inhbition *vs* CLcr





Drug-Drug Interactions

a) ***Is there an in vitro basis to suspect in vivo drug-drug interactions? is the drug a substrate of CYP enzymes? is the drug an inhibitor and/or an inducer of CYP enzymes?***

PS-341 is primary a substrate of CYP 3A4. Drugs that are substrates, inhibitors or inducers of 3A4 may inhibit or induce its metabolism (see Phase 4 Commitments). The package insert will include a precaution statement for the use of VELCADE in combination with drugs that are substrates, inhibitors or inducers of 3A4 and substrates.

In vitro Inhibition:

In vitro studies with human liver microsomes indicate that PS-341 at concentrations ranging from _____ may be a weak inhibitor of CYP1A2, 2C9, 2D6, and 3A4 activities; the IC_{50} values were > 30 μM (> 11.5 μg/ml). These IC_{50} values were

higher than those reported for positive controls ***(Report RPT-00135)***. The maximum PS-341 concentrations obtained in MM patients at the proposed 1.3 mg/m^2 dose ranged from ———. PS-341 is unlikely to affect the metabolic clearance of concomitantly administered drugs that are substrates of 1A2, 2C9, and 2D6.

Table 13. IC_{50} values for CYP isozymes in human liver microsomes (in Triplicates)

CYP Substrates	Stud. Conc, (μM)	*Optimum Substrate Conc. (μM)	PS-341 (μM)	Positive Controls				
				Furafylline (μM)	Sulfaphen-azole (μM)	Omepra-zole (μM)	Quinidine (μM)	Keto-Conazole (μM)
Phenacetin (1A2)	120	≤100	> 30	3.2				
Tolbutamide (2C9)	600	<500	> 30		0.17			
S-Mephenytoin (2C19)	400	<200	18			3.3		
Dextromethorphan (2D6)	32	<50	> 30				0.09	
Testosterone (3A4)	200	<250	> 30					0.6
Midazolam (3A4)	100	<10	> 30					0.5

*(Draft Mapp - *In vitro* metabolism/transport, Part I-A CYP inhibition (May 7, 2002, pp 3)

In the above table, it is noted that the *in vitro* substrate concentrations studied were within the optimum substrate concentrations for dextromethorphan (2D6) and testosterone (3A4) according to the draft *in vitro* metabolism/transport Mapp. *In vitro* substrate concentrations studied were close to the optimum substrate concentrations for phenacetin (1A2) and tolbutamide (2C9). However, because the IC_{50} values were > 30 μg/ml which are much higher than maximum PS341 in vivo concentrations (1.3 μg/ml), there is no potential for PS341 to inhibit the activity of these enzyme at the therapeutic concentrations.

In vitro substrate concentrations were about 10-fold higher than the optimum substrate concentration for midazolam (3A4) (100 μM vs <10 μM) for *in vitro* inhibition studies. As midazolam is a more sensitive substrate than testosterone, the Applicant should repeat the *in vitro* microsomal studies at appropriate midazolam concentrations (<10 μM) to properly assess the inhibitory potential of PS-341 on 3A4 (see Phase 4 Commitments).

An IC_{50} value of 18 μM was obtained at an *in vitro* substrate concentration 2-fold higher than the optimum substrate concentration for S-mephenytoin (2C19) (400 μM vs <200 μM) for *in vitro* inhibition studies. There may be a possibility that PS-341 inhibits 2C19 activity. At this optimum substrate concentration (<200 μM); PS-341 IC_{50} value may be close the reported one for omerprazole, the positive control (3.3 μM). Thus, PS-341 may have the potential to decrease the metabolic clearance of concomitantly administered drugs that are substrates of 2C19 activity. The Applicant should repeat the *in vitro* microsomal studies at appropriate S-mephenytoin concentrations (<200 μM) to properly assess the inhibitory potential of PS-341 on 2C19 (see Comments to the Applicant).

Induction:

PS-341 does not induce the activities of CYP 3A4 and 1A2 in primary cultured human hepatocytes ***(RPT-00021)***. Human livers were obtained from two donors (57- and 61-year

Caucasian females). Confluent hepatocyte monolayers were incubated with PS-341, omeprazole, or Rifampin for 48 hours (in triplicates) and the CYP1A2 and 3A4 activities in the hepatocytes were determined by O-deethylation of ethoxyresorufin and 1-hydroxylation of midazolam, respectively.

Table 14. Mean % of CYP activity (Treatment/Control)

Human Liver #1			
CYP 1A2 Activity (% Control)		CYP 3A4 Activity (% Control)	
50 µM omeprazole	890	25 µM Rifampin	3632
2.5 µM PS-341	150	2.5 µM PS-341	30
5 µM PS-341	160	5 µM PS-341	15
10 µM PS-341	180	10 µM PS-341	10
25 µM PS-341	200	25 µM PS-341	4
50 µM PS-341	200	50 µM PS-341	2
Human Liver # 2			
CYP 1A2 Activity (% Control)		CYP 3A4 Activity (% Control)	
50 µM omeprazole	500	25 µM Rifampin	270
2.5 µM PS-341	115	2.5 µM PS-341	35
5 µM PS-341	125	5 µM PS-341	25
10 µM PS-341	135	10 µM PS-341	20
25 µM PS-341	135	25 µM PS-341	10
50 µM PS-341	160	50 µM PS-341	3

The data in the above table also indicate that PS-341 may inhibit the 3A4 activity when using cultured human hepatocytes, 3-35% at PS-341 concentrations of 2.5-50 µM (see Phase 4 Commitments).

b) ***Is the drug a substrate and/or an inhibitor of P-glycoprotein (P-gp) transport processes or other metabolic/transporter pathways that may be important?***

The Applicant claims that PS-341 is not a substrate of P-gp based on *In vitro* permeability studies using P-gp expressed Caco-2 cell monolayer studies ***(RPT-00013)***. Transfected Caco-2 cell monolayers were used to determine the permeability of PS-341, propranolol (positive control), and lucifer yellow (negative control) in both the apical to basolateral (A to B) and the basolateral to apical (B to A) directions.

Table 15. Permeability of PS-341 and Permeation Markers Across Caco-2 Cell Monolayers

Compound	In vitro concentration	Papp, nm/sec[a]		
		A-B	B-A	B-A/A-B ratio
PS-341	50 µM	292	382	1.31
Propranolol	50 µM	647	554	0.86
Lucifer Yellow	50 µM	<20	<20	1.0

a Ranges low permeability = <50 nm/sec, medium permeability = 50-200 nm/sec, high permeability = >200 nm/sec. (Experiments made in doubles)

PS-341 has a reasonably high permeability (> 200 nm/sec) with a B-A/A-B permeability ratio of 1.31. However, in the absence of permeability data for a P-gp sensitive substrate such as Rhodamine123 or digoxin, it is not possible to conclude that PS-341 is not a P-gp substrate. The permeability of propranolol or lucifer yellow is not influenced by P-gp efflux pump. The Applicant performed some studies with vinoblastine, a P-gp substrate, and found that the

B-A/A-B permeability ratio is 8-10 (data were not submitted) (see Comments to the Applicant).

c) ***What other co-medications are likely to be administered to the target patient population (i.e., patients with multiple myeloma?***

The co-medications that are likely to be administered with VELCADE in MM patients may include beta-blockers (e.g., S-metoprolol, timolol), macrolide antibiotics (e.g., erythromycin), calcium channels (e.g., sildenafil, verapamil, nifedipine), and St. John's Wort. These drugs are mostly substrates, inhibitors, or inducers of 3A4. To date, the applicant did not conduct or plan to conduct any drug interaction studies with any of these drugs.

d) ***Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?***

The Applicant did not conduct or plan to conduct any formal drug-drug interaction study. However, As PS-341 is primary a substrate of CYP 3A4. The label will include a precaution for the use of VELCADE in combination of drugs that are substrates, inhibitors or inducers of 3A4. Unresolved drug interactions still remain (see Phase 4 Commitments). The ongoing population PK analysis of the Phase 3 data (Study M34101-39) may examine the effect of concomitant medication as one of the covariates.

e) ***Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?***

The Applicant conducted *in vitro* metabolism, *in vitro* CYP inhibition, and protein binding studies for PS-341. At this time, there are no unresolved questions related to *in vitro* metabolism, active metabolites, or protein binding. However, the primary CYP enzyme involved in PS-341 metabolism is CYP 3A4. The Applicant should conduct formal PK and PK/PD studies to determine the potential for drug-drug interactions between PS-341 and drugs that are inhibitors or inducers of 3A4 (see Phase 4 Commitments). The Applicant has not characterized the disposition of PS-341 in MM patients. The labeling will indicate that the disposition of PS-341 in humans has not been characterized until this information is submitted to the agency (see Comments to the Applicant).

f) ***What issues related to dose, dosing regimens or administration are unresolved, and represent significant omissions?***

No specific dosing recommendations could be made for in the label for renally or hepatically impaired patients (see Phase 4 Commitments). Interaction studies between PS-341 and inhibitors or inducers of CYP 3A4 are recommended to provide proper dosing for labeling considerations (see Phase 4 Commitments).

E. General Biopharmaceutics

As PS-341 is administered as an IV bolus, the Applicant does not have to conduct any bioavailability, bioequivalence, or food effect study.

F. Analytical Section

The Applicant measured PS-341 [redacted]

[redacted] the method was not adequately validated (no quality control data available) (Table 16).

Table 16. Validation of LC/MS/MS analytical method for analysis of PS-341in plasma samples

Studies	Internal standard	LOQ* (ng/mL)	Linear Range (ng/mL)	Between Run Precision (%CV)	Between Run Accuracy (%)	% CV for QC samples	Specificity
DM98-194	[redacted]	[redacted]	[redacted]	2.7-7.7%	85-104%	ND	No Interference
M34100-024 M34100-025	[redacted]	[redacted]	[redacted]	2.03-9.9%	98-102%	<10% at 1.5, 10, and 25 ng/ml	No Interference

*LOQ Limit of quantitation ND (not determined)

A detailed description of the assay method and a summary performance of quality control samples are presented in Appendix 3.

VI. OCPB'S Labeling Recommendations

[Note: Statements to be added are in italic and bold. Statements to be deleted are double-strikeout]

CLINICAL PHARMACOLOGY

Pharmacokinetics

[redacted]

Following intravenous administration of 1.3 mg/m^2 dose, the median estimated maximum plasma concentration of bortezomib is 509 ng/ml (range=109-1300 ng/ml) in eight patients with multiple myeloma and creatinine clearance values ranging from 31-169 ml/min. The mean elimination half-life of bortezomib after first dose ranged from 9 to 15 hours at doses ranging from 1.45 to 2.00 mg/m^2 in patients with advanced malignancies.

Metabolism

In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 (CYP) isozymes indicate that bortezomib is primarily oxidatively metabolized by CYP 1A2, 2C9, 2C19, 2D6, and 3A4 enzymes. The major metabolic pathway is deboronation to form metabolites two deboronated metabolites which are subsequently hydroxylated to several metabolites. Deboronated-bortezomib metabolites are inactive as 26S proteasome inhibitors. Pooled plasma data from eight patients at 10 min and 30 min after dosing indicate that the metabolites plasma levels are low compared to the parent drug.

APPENDIX 1

Office of Clinical Pharmacology and Biopharmceutics Review: Pharmacometrics

NDA:	**21-602**
Compound:	**Velcade (Bortezomib, PS-341)**
Submission Date:	**Dec 31, 2002**
Applicant:	**Millennium Pharmaceuticals, Inc.,**
Pharmacometrics Reviewer:	**Joga Gobburu**

Introduction

The applicant performed sub-minimal characterization of the pharmacokinetics of Velcade. Essentially no pharmacokinetic information was collected in the pivotal studies 024 and 025. In the animals, the drug is shown to be cleared both by hepatic and renal routes (21%).

The primary review dealt with the concentration-proteasome inhibition relationship and will not be part of the current pharmacometrics review. The pharmacometrics review will focus on the dose-response relationships for the effectiveness and safety variables. Complete response based on 3 different criteria were identified by the applicant, retrospectively, namely: Blade, SWOG and that which does not require immunofixation (IF). The response data were provided by Dr. Peter Bross, Medical Reviewer. Potential toxicity variables explored by this reviewer include: diarrhea, thrombocytopenia, nausea and neuropathy.

At this time, the reviewer is still waiting for a list of concomitant drugs administered to the patients in studies 024 and 025.

Methods

Data

Study 024

This was an open- label, multi- center study designed to evaluate the efficacy and safety of PS-341 administered at doses of 1.0 and 1.3 mg/ m^2 given alone, or in combination with dexamethasone subsequent to inadequate response to PS- 341 monotherapy, administered to patients with multiple myeloma who had failed to respond to or had relapsed following either conventional or high- dose front- line therapy. A treatment cycle was comprised of four injections of PS- 341 (on Days 1, 4, 8, and 11) followed by a 10- day rest period; a maximum of up to 8 cycles of treatment could be administered. After Cycle 2, patients with progressive disease on PS- 341 were allowed to have dexamethasone added to the patient's treatment regimen. After Cycle 4, patients with stable disease on PS- 341 were also allowed to have dexamethasone added. A total of 64 patients were planned; 54 patients were enrolled and treated including 28 patients treated at 1.0 mg/ m 2 and 26 patients treated at 1.3 mg/ m^2. Patients were to receive a maximum of eight 3- week treatment cycles; therefore, the maximum duration of treatment in this study was 24 weeks (~ 6 months). Responding patients were allowed entry into the extension study M34100- 029 to receive additional PS- 341.

Study 025

This was an open- label multi- center study conducted between 26 February 2001 and 12 June 2002 at 14 study centers in the US. A treatment cycle was comprised of 4 injections of PS- 341 (on Days 1, 4, 8, and 11) followed by a 10- day rest period; a maximum of up to 8 cycles of treatment could be administered. During all treatment cycles, patients were to receive PS-341 1.3 mg/ m^2. After Cycle 2, patients with progressive disease on PS- 341 were allowed to have dexamethasone added to the patient's treatment regimen. After Cycle 4, patients with no change in disease status on PS- 341 were also allowed to have dexamethasone added to the PS-341 treatment regimen.

A total of 202 patients were enrolled in this study including 78 patients enrolled in the original protocol (designated Cohort 1) plus an additional separate cohort of 124 patients added by protocol amendment (designated Cohort 2). Cohort 2 was added because enrollment was so rapid that many initiated centers were unable to begin enrollment before the original sample size had been met. The initial cohort of 78 patients, which was enrolled over 5 months, was based on all patients who received their first dose of PS- 341 as of 23 July 2001; all patients in Cohort 2 were enrolled subsequent to that time. The primary conclusions regarding treatment efficacy, as prospectively defined in the protocol, were to be based on the initial planned cohort of patients, with corroborative evidence of effectiveness and characterization of the safety profile derived from the second cohort.

Table 1 shows the demographic data for the patients enrolled in studies 024 and 025.
Models

Exposure

Essentially no pharmacokinetic information is collected in the studies 024 and 025. In study 025, 8 patients out of 202 provided very sparse PK information. For that reason dose was the only measure of exposure used.

Table 1. Demographics of the patients enrolled in studies 024 and 025. The number of subjects (with data), median, 25th (Q25) and 75th (Q75) quartiles are shown. Key: BSA=body surface area; CLCR=creatinine clearance; Spa1=specific activity of proteasome; cht1=proteasome activity quantitated by chymotryptic to tryptic ratio.

Variable	Units	N	Median	Q25	Q75
Weight	Kg	258	77.10	67.10	88.20
Age	Years	256	60.00	53.00	68.00
Height	cm	258	167.64	160.02	175.26
BSA	m^2	258	1.90	1.72	2.06
CLCR[a]	mL/min	255	74.24	56.27	100.21
Spa1	%	188	60.87	54.75	68.79
Cht1	%	187	61.02	51.64	70.09
Prior Regimens	number				
Categorical Variables					

Males		144	
Female		112	
Whites		213	82%
Blacks		27	10%
Ondansetron		84	32%
Anti-Emetics		138	53%
Opioids		166	64%
Renal Impairment			
	Mild		40%
	Moderate		16%
	Severe		6%

[a] CLCR was calculated using the Cockraft-Gault equation. Any CLCR value more than 120 mL/min was considered as 120 mL/min.

Effectiveness

Logistic regression was performed to correlate dose and other demographic variables with effectiveness endpoints (Blade, IF and SWOG). Data from the studies 024 and 025 were combined.

Toxicity

Logistic regression was performed to correlate dose and other demographic variables with toxicity variables (diarrhea, thrombocytopenia, nausea and neuropathy). Where applicable two types of analyses were conducted. The first type of analysis used safety data as an yes or no answer: Was there diarrhea or not? The second type included data with the worst grade of the toxicity for each patient. Data from the studies 024 and 025 were combined.

Results

Effectiveness

None of the 3 endpoints were correlated to the dose and any of the demographic variables, when data from studies 024 and 025 were combined. There could be several reasons for the lack of any correlation. Some of them include: 1) small effect size, 2) small sample size given the effect size (only about 10% of the total population received the lower dose), and 3) effect reached plateau at the lower dose. It is almost impossible to discern which of these is relevant for the current data. The data suggest that the inhibitory effect of Velcade on proteasome enzyme reaches maximal effect at about 1 mg/m^2. No additional effect on this biomarker can be expected at 1.3 mg/m^2. The applicant claims that there are more patients with complete, partial and minimal responses (pooled) in the 1.3 mg/m^2 when compared to 1 mg/m^2 group. In spite of having a wide range of effects on the proteosome inhibition, no correlation between this biomarker and the response could be found. It is not clear whether the wide variation in the suppression of proteosome activity (almost from negligible to complete suppression) is due to sampling time deviations or not. If it is not due to sampling errors then evidently there is no basis for the choice of 1 and 1.3 mg/m^2 doses. There is a suggestion that dexmethasone intake is correlated negatively with response rate, which is expected. Patients who either progressed after two cycles or had stable disease after 4 cycles received dexmethasone (40 mg) as rescue therapy.

When the data from study 025 were analyzed separately, it was found that more percentage of blacks responded compared to other races. Blacks have 3-fold higher probability of responding to Velcade. At this point this finding should only be hypothesis generating. Analysis of future trials should explore this issue further.
Safety

Diarrhea
Yes or No Analysis

Dose was found to be correlated to the incidence of diarrhea (of any grade). The higher dose (1.3 mg/m^2) has 10 times higher probability of diarrhea than the lower dose. No other demographic variable was found to be important.

Table 2. Logistic regression parameter estimates for diarrhea (yes or no analysis).

Total Observations	Parameter	Estimate (± SE)	P-value	Odds Ratio[a]
255	Intercept	-4.83 ± 2.04	0.0181	-
	Dose	3.53 ± 1.60	0.0270	10

[a] since the original odds ratio reflects the odds of the risk for doubling the dose, the odds ratio was adjusted to reflect the odds for the 1.3 mg/m^2 dose.

Worst Grade Analysis

Table 3 shows the logistic regression parameter estimates for diarrhea, evaluated as a graded response. The odds ratio for the dose reflects that patients receiving the higher dose are at 16 times higher risk than those at the lower dose. No other demographic variable was found to be important.

Table 3. Logistic regression parameter estimates for diarrhea (Worst Grade Analysis). Diarrhea was scored as toxicity grades 0 (no event) through 4 (severe).

Total Observations	Parameter	Estimate (± SE)	P-value	Odds Ratio[a]
255	Prob (=4)	-9.87 ± 2.21	<0.0001	-
	Prob (≥3)	-7.73 ± 2.11	0.0003	
	Prob (≥2)	-6.42 ± 2.10	0.0022	
	Prob (≥1)	-5.33 ± 2.09	0.107	
	Dose	3.93 ± 1.63	0.0160	16

[a] since the original odds ratio reflects the odds of the risk for doubling the dose, the odds ratio was adjusted to reflect the odds for the 1.3 mg/m^2 dose.

Thrombocytopenia

Patients who received granulocyte colony stimulating factor (GCSF) or patients who are males had higher incidences of thromobocytopenia. Patients who received GCSF have about 2-fold higher probability of thromobocytopenia. Patients receive GCSF to preserve the WBC count, but this has makes the platelet count to go down. Males are at higher risk of thrombocytopenia than females by 70%. It is possible that per m^2 dosing (note: BSA

calculation uses total body weight) leads to inappropriately higher exposures in males. The difference between ideal body weight and total body weight was 22 kg in females and 25 kg in males, for those whose ideal body weight is greater than 120% of their ideal body weight (criteria for obesity). The 25% and 75% percentiles of the total body weight in this set of patients, is 67-85 kg in females and 86-108 kg in males. More percentage of male patients (56%) received GCSF than females (44%). Mechanistic reason for why males are more prone to thrombocytopenia is not obvious. Nevertheless, males indeed have higher incidences.

Table 4. Logistic regression parameter estimates for thrombocytopenia (yes or no analysis).

Total Observations	Parameter	Estimate (± SE)	P-value	Odds Ratio
256	Intercept	-1.12 ± 0.24	0.0001	-
	GCSF	0.85 ± 0.27	0.0017	2.34
	Males	0.56 ± 0.27	0.0394	1.74

Nausea
Yes or No Analysis

Dose and ondansetron (anti-emetic) were found to be important predictors of nausea. Patients who received ondansetron had 1.8-fold higher probability of nausea. Ondansetron is a CYP2D6 substrate and there is suggestion that Velcade is partly metabolized by CYP2D6. An important aspect that should be noted is the unaccounted time difference between intake of ondansetron and occurrence of nausea. Whether the positive correlation between ondansetron intake and Velcade intake is because of the metabolic interaction (whereby the exposure of Velcade increases) or a natural consequence of symptom treatment cannot be resolved. Most probably the finding suggests that ondansetron is given to patients who had symptoms of nausea or emesis. This particularly true since for the other AEs intake of ondansetron was not found to be important. Had it been a metabolic interaction, this should have showed up positive for other AEs as well. In order to explore this issue further, a variable signifying whether a patient received any anti-emetic, not just ondansetron, was introduced. The analysis suggested that in general taking any anti-emetic is positively correlated with the probability of nausea. Patients administered with the higher dose are at 15-fold higher risk than the lower dose.

Table 5. Logistic regression parameter estimates for nausea (yes or no analysis).

Total Observations	Parameter	Estimate (± SE)	P-value	Odds Ratio [a]
256	Intercept	-4.98 ± 1.89	0.0083	-
	Ondansetron	0.57 ± 0.28	0.0394	1.8
	Dose	3.87 ± 1.48	0.0088	15

[a] since the original odds ratio reflects the odds of the risk for doubling the dose, the odds ratio was adjusted to reflect the odds for the 1.3 mg/m^2 dose.

Worst Grade Analysis

Again, dose and ondansetron intake were found to be the important predictors for nausea, when the worst grade for each patient was considered. The final parameter estimates are shown in Table 6.

Table 6. Logistic regression parameter estimates for nausea (Worst Grade Analysis). Nausea was scored as toxicity grades 0 (no event) through 3 (severe).

Total Observations	Parameter	Estimate (± SE)	P-value	Odds Ratio [a]
255	Prob (≥3)	-8.11 ± 2.11	0.0001	
	Prob (≥2)	-6.42 ± 2.10	0.0004	
	Prob (≥1)	-5.33 ± 2.09	0.0043	
	Ondansetron	0.65 ± 0.25	0.0089	2
	Dose	4.17 ± 1.47	0.0046	16

[a] since the original odds ratio reflects the odds of the risk for doubling the dose, the odds ratio was adjusted to reflect the odds for the 1.3 mg/m^2 dose.

Neuropathy
Yes or No Analysis

None of the factors explored provided consistent correlation with the probability of neuropathy. There is some indication that in patients with mild or moderate renal impairment the probability of neuropathy is higher, but not in severe. It is intriguing why. One possibility that was considered is the rather small number of patients with severe renal impairment (about 6%). Considering moderate and severe renal impairment together did not result in significant effects. Nevertheless, dose was not found to be an important predictor of neuropathy.

Worst Grade Analysis

Dose was not found to be an important predictor of neuropathy.

Constipation
Yes or No Analysis

Dose was not found to be correlated with constipation. Velcade causes pain (e.g.: neuropathy) and the patients, as a consequence, receive opioids for symptomatic relief. Opioids, such as morphine, are known to cause constipation. As expected opioid intake is the strongest predictor of constipation, followed by whether a patient has severe renal impairment. About 64% of patients in both the dose groups received opioids (i.e., no dose dependency). This finding is congruent with the previous analysis where dose was not found to be correlated with neuropathy, if we were to assume neuropathy to be a precursor to receive opioids. Black patients seemed to have 1/3rd the incidences of constipation than other races.

Table 7. Logistic regression parameter estimates for constipation (yes or no analysis).

Total Observations	Parameter	Estimate (± SE)	P-value	Odds Ratio
256	Intercept	-0.81 ± 0.23	0.0005	-
	Opioid intake	0.98 ± 0.28	0.0005	2.7
	Severe Renal Impairment	1.83 ± 0.83	0.0283	6.2
	Black	-1.08 ± 0.47	0.0214	0.3

Conclusions

1. None of the 3 effectiveness endpoints were correlated to the dose and any of the demographic variables. There could be several reasons for the lack of any correlation. Some of them include: 1) small effect size, 2) small sample size given the effect size (only about 10% of the total population received the lower dose), and 3) effect reached plateau at the lower dose. In study 025, more percentage of blacks seemed to respond compared to other races.
2. (Send to applicant) Interestingly, given a high enough doses (with respect to proteasome inhibition) there seems to be wide range of effects ranging from below zero to about 100% inhibition, in studies 024 and 025. One practical reason could have been that although the protocol specified a 1hr sample, it is possible that the actual time could be off. Given the rapid disposition phase of Velcade, such large variability is possible should the sampling time be mislabeled. The applicant should explain this result.
3. (Send to applicant) Two points need to be noted regarding body size based dosing: a) between patient variability and b) mechanistic reasoning. a) Even given the little PK information, the variability seems to be as high as 80% for the important PK parameters like initial concentration and clearance (Study DM98-194, dose=1.6 mg/m^2, N=13). If this estimate of between subject variance is accurate, it is not clear why Velcade needs to be dosed based on body surface area. It is unlikely that body size explains significant portion of the unexplained variability. b) The toxicity seems to be dose dependent and no explanation is given by the sponsor whether the dose needs to be given on a per m^2 basis. If the drug is not well distributed into poorly perfused tissues (eg: adipose), then indeed the dose should not be based on total body size. The applicant should substantiate the need for body size based dosing. Future studies should use the appropriate dosing scheme.
4. Diarrhea and nausea were found to be dose-related.
5. Patients who received granulocyte colony stimulating factor (GCSF) have higher incidences of thromobocytopenia.
6. The lack of convincing dose-effectiveness relationship limits the ability to suggest rational dosing for Velcade. Very clearly, the 1.3 mg/m^2 group had higher toxicity, but no advantage for the response rate (effectiveness) was evident. In the study 025, in a considerable fraction of patients the dose was reduced to 1 mg/m^2 from 1.3 mg/m^2. One could speculate that in clinical practice this fraction could be even more. It is only prudent for the sponsor to find the rational dose towards more meaningful labeling of Velcade. Approach to finding a 'rational' dose for Velcade needs some discussion. The analysis presented by this reviewer did not establish that proteosome inhibition is a good predictor of the response rate. In fact some patients with negligible inhibition (assuming the inhibitory effect is appropriately measured) responded, based on the SWOG criteria. Hence targeting a dose of 1mg/m^2 itself is questionable. It is possible that lower doses

could have produced similar response rates as for the 1.3 mg/m^2 dose, but with lower toxicity. Closer look at the SWOG responses showed that a majority patients achieved this response by the second cycle, and few more by the fourth cycle. The applicant should conduct a randomized dose ranging study including 0.7 mg/m^2, 1.0 mg/m^2 and 1.3 mg/m^2. If the patients who receive the lower doses do not respond (according to the SWOG criteria) by the fourth cycle, they might be transferred to the next higher dose group. Also, the applicant should collect pharmacokinetic data in future studies to enable rational dosing strategies. Such a study should provide valuable data to select an optimal dosing scheme for labeling. The application should consider such a study.

Recommendations

1. Reviewer comments #2, #3 and #6 should be forwarded to the applicant.

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/s/

Peter Bross
5/8/03 11:54:07 AM
MEDICAL OFFICER

VELCADE NDA review

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5/8/03 12:43:40 PM
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