Reviewer comment: "QOL" (patient reported outcome) studies are exploratory only and are not acceptable for registration purposes in a single arm study.

3.7.2 Drug levels and pharmacokinetic assessments

(Dana Farber Cancer Institute only) Serial blood samples will be collected from patients participating in the study at the Dana Farber Cancer Institute for determination of plasma PS-341 levels immediately before and at 2, 5, 10, 15, 30, 60, and 120 minutes and 24 hours after PS-341 administration on Day 1, Cycle 1.

3.7.3 Pharmacodynamic measurements

The pharmacodynamics of PS-341 will be determined for each patient using the 20S proteasome assay. Blood samples for the proteasome inhibition assay will be obtained from all patients before and one hour after PS-341 dosing on Days 1 and 11 of Cycles 1, 7, and, if applicable, the cycle in which dexamethasone is started. This *ex vivo* assay measures proteasome inhibition, the molecular target of PS-341. Patients participating in the study at the Dana Farber Cancer Institute will have an additional sample collected for the proteasome inhibition assay at 24 hours after dosing on Day 1, Cycle 1. Assays will be performed at Millennium.

3.7.4 Pharmacogenomic assessments

In patients who consent to participate (via a separate consent form for this procedure), blood and bone marrow samples will be obtained and tested for the expression of global mRNA levels and proteins. These samples (i.e., both bone marrow and blood) should be provided from evaluations conducted at the Screening visit and at any time bone marrow specimens are obtained. Assays will be performed at Millennium.

3.7.5 Neurophysiological assessments (Dana Farber Cancer Institute only)

Neurophysiological testing will be performed for patients participating in the study at the Dana Farber Cancer Institute before study drug administration on Day 1, Cycle 1, and on Day 1 of every other treatment cycle thereafter (Cycles 3, 5, and 7). Neurophysiological testing also will be performed for patients who develop neuropathy at any time during the study as well as for patients who develop neuropathy within two to three months after completing treatment in order to assess the presence of a coasting effect and the time to improvement.

Neurophysiological testing will include motor and sensory nerve conduction studies (NCS) as follows: sural NCS on both legs, peroneal and posterior tibial motor NCS on one leg, radial and ulnar sensory NCS on one arm, and ulnar motor NCS on one arm. In addition, quantitative sensory testing (QST) of vibratory, heat, and cold perception in one hand and one foot. Sympathetic skin responses (a measure of autonomic function) will be performed in both feet.

Skin biopsies will be performed on a voluntary basis for patients who provide written informed consent via a separate informed consent form at the Screening visit. Skin biopsies also will be

performed at the End of Study visit for patients who developed signs of peripheral neuropathy during the study. Skin biopsies will be immunostained, and the number of small myelinated nerve fibers will be quantified. This is a sensitive indicator of peripheral neuropathy, particularly small fiber neuropathies. Details regarding skin biopsy handling and processing are provided in the Study Manual.

3.8. Follow-up/safety considerations

3.8.1 Screening visit

A medical history, vital signs, and a complete physical examination will be conducted during the Screening visit and at the End of Study visit to evaluate any changes from baseline status. A 12-lead ECG and posteroanterior and lateral chest x-rays will be obtained during the Screening visit. These assessments should be repeated during the treatment period if screening results are abnormal and/or if clinically indicated for the management of new or worsening symptoms.

3.8.2 Follow-up clinic visits:

Interval histories will be collected and directed neurotoxicity questioning and symptom-directed physical examinations will be performed weekly during treatment on Days 1 and 11 of each cycle.
Vital signs, including heart rate, respiratory rate, blood pressure and temperature, will be obtained before and 1 and 2 hours after each dose of study drug in each treatment cycle. End of Study visit. After the End of Study visit, directed neurotoxicity questioning is to be performed on an every six-week basis only until development of confirmed PD (or relapse) for patients who have not experienced confirmed PD (or relapse) on their most recent study drug regimen (PS-341 alone or PS-341 plus dexamethasone).

3.9. Laboratory assessments

3.9.1 Routine Laboratory Assessments

Blood samples for analysis will be drawn at the Screening visit, before PS-341 administration on Days 1, 4, 8, and 11 of each cycle, and at the End of Study visit. The results obtained before each dose must be available and reviewed by the investigator before dosing with PS-341 to evaluate for possible toxicity.

Hematology including Hematocrit/Hemoglobin/ RBC count WBC count with differential and circulating plasma cells (by peripheral blood film) and Platelet count

Biochemistry including Electrolyte Panel (Sodium Potassium Chloride Glucose Calcium) and chemistry panel: (BUN Alkaline phosphatase Serum creatinine Lactate dehydrogenase (LDH) Uric acid Aspartate transaminase (AST, SGOT) Bilirubin (total) Alanine transaminase (ALT, SGPT) Total Protein and Albumin)

3.9.2 Laboratory Efficacy Assessments:

Serum protein electrophoresis with quantitation of immunoglobulins and immunofixation as well as a 24-hour urine specimen collected and adequately concentrated for electrophoresis with immunofixation will be collected at the Screening visit; between Days 15 and 18 of the rest period during Cycles 2, 4, and 6; and at End of Study visit. After the End of Study visit, these evaluations are to be performed on an every six-week basis only until development of confirmed PD (or relapse).

3.9.3 Bone marrow analysis

Bone marrow aspirates and biopsies are to be obtained in all patients at the screening visit, and at the time of first response in patients who achieve a CR by immunofixation and then six weeks later to confirm response. If immunofixation tests remain negative at subsequent timepoints, then bone marrow aspirates and biopsies need not be repeated. Bone marrow samples will be evaluated to determine the percentage of plasma cells in the bone marrow. In addition, bone marrow samples will also be evaluated for plasma cell labeling index (PCLI) and for the presence of any cytogenetic markers. In patients who achieve a complete response to treatment, bone marrow will also be examined by polymerase chain reaction (PCR) technology for the presence of the patient specific monoclonal Ig rearrangements present as a marker of the disease to assess remission at a molecular level. In addition, for patients who are willing and sign a separate consent form, a bone marrow sample will be obtained for pharmacogenomics.

3.9.4 Skeletal Survey

A roentgenographic survey of bones including humeri and femora will be obtained during the Screening visit to document bony abnormalities, i.e., lytic lesions. If the screening results are abnormal, the survey should be repeated every four cycles and at the time of response (if applicable). In addition, a skeletal survey should be conducted in any patient who develops new bone pain, unless clearly unrelated to myeloma.

3.9.5 Other laboratory Assessments

Samples for β2 microglobulin, C-reactive protein, and IL-6 are to be obtained before study drug administration on Day 1 of Cycles 1, 3, 5, and 7, and at the End of Study Visit.

3.10. Endpoints: safety data

3.10.1 Adverse events

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study drug related. This includes any newly occurring event

or previous condition that has increased in intensity or frequency since the administration of study drug.

3.10.2 Serious adverse events

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death.
- Is life-threatening. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned before study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected manner during the study (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a persons' ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs.

3.11. Statistical and analytic considerations:

3.11.1 Sample size estimates

This study will enroll a total of up to 75 patients into the original study cohort. This sample size estimate is based on the desire to determine if the true rate of response to PS-341 alone is at least 10%, at the one-sided alpha-level of 0.05 and having at least 80% power to conclude the rate of response is 20% or more. An additional cohort of up to 125 patients may be enrolled. It is not intended that patients enrolled into the second cohort be used to replace any patients who may discontinue prematurely from the first cohort.

3.11.2 Population for Analysis

The Intent-to-Treat (ITT) population of patients will be defined as all patients who receive at least one dose of study drug. The primary efficacy results in the study will be based on data from patients in the ITT population who had measurable disease at the Screening visit. Patients in this population who have inadequate data post-baseline to assess efficacy according to the criteria for response in Table 1 will be considered treatment failures for this analysis. Patients in

this population will be analyzed according to the treatment they were actually scheduled to receive, regardless of any errors of dosing or dose modifications.

A Per-Protocol (PP) set of patients will be defined as all patients who are 90% compliant with study drug dosing for at least one full treatment cycle and who have no major protocol violations. Major violations may include violations of one or more of the inclusion and exclusion criteria, failure to complete at least study evaluations at baseline and at 21 days after Day 1 of the first dose (within pre-defined time windows), receipt of restricted concomitant medications that would interfere with drug evaluation (but not as a consequence of treatment failure), and other major violations that may be determined after data collection but before database lock. A comparison of results between the full analysis set and the per-protocol set will be made and differences in results will be discussed. The PP population will be used for analysis only if this subset includes a number of patients that is no greater than 85% of the size of the ITT population.

The two regimens will be assessed for comparability of demographic and baseline characteristics, in a descriptive, exploratory fashion only. The purpose of this comparison is to examine if any characteristics may predispose patients to require combination therapy. Data to be evaluated will include at least age, gender, race, and components of disease severity assessment.

3.11.3 Efficacy Analysis: response rates

The investigator will evaluate each patient for response to therapy according to SWOG criteria augmented from those developed by Blade *et al.*, 1998 presented in Table 1. Assessment of disease response will be performed on Day 1 of Cycles 3, 5, and 7; and at the End of Study visit.

After the End of Study visit, this evaluation is to be performed on an every six-week basis only until development of confirmed PD (or relapse) for patients who have not experienced confirmed PD (or relapse) on their most recent study drug regimen (PS-341 alone or PS-341 plus dexamethasone). Disease response is to be assessed primarily by measurement of serum or urine M-protein and/or serum calcium, if possible. However, patients with non-secretory MM will require additional procedures (e.g., skeletal survey, bone marrow aspirate and biopsy) to determine PD. If a patient is determined to have CR, PR, or MR, then assessment of disease response is to be performed six weeks later to confirm the response.

Efficacy analyses on disease response (rates of responders to the initial regimen of PS-341, where a responder is defined as a CR, PR, or MR; rates of CR; time to and duration of response; time to disease progression) will be based primarily on the results of the IRC's independent majority disease response assessment (see Section 3.6.1). Additional analyses may be produced using the investigator-determined disease response.

The primary efficacy analysis will be performed on the ITT population rate of responders, where a responder is defined for this analysis as a patient who achieves a CR, PR or MR from PS-341 alone, using the criteria prospectively established in Table 1 in Section 3.6.1. One-sided 95% confidence limits on the lower limit of the percentage of responders will be established to

determine if this lower bound exceeds 10%. The same method of analysis using confidence intervals will be presented for rates of CR to PS-341 alone. In this analysis, all patients who fail to respond to PS-341 alone, regardless of their potential subsequent response to the combination therapy, will be considered treatment failures. A secondary analysis will be performed that establishes a similar confidence limit for responders to the combination of PS-341 with dexamethasone. This analysis will yield only a conditional estimate for the rate of response to the combination, since only patients who previously fail to respond to PS-341 will be eligible. The number and percent of patients meeting each disease response category, as presented in Table 1, will be descriptively tabulated for each cycle. For the category PR, a subset will be presented for the number and percent of patients experiencing remission, defined as meeting all criteria for PR but exhibiting a ≥75% reduction in the level of serum monoclonal protein for at least two determinations six weeks apart. A subset also will be presented for the number and percent of patients experiencing "near complete response", defined as meeting all criteria for PR but exhibiting a ≥90% reduction in the level of serum monoclonal protein for at least two determinations six weeks apart.

3.11.4 QOL endpoints

Measurement of quality of life (QOL) has gained widespread acceptance as a means of assessing the effects of chronic illness on a patient's well being. Four QOL instruments will be evaluated in this study, the EORTC QLQ-C30 and EORTC QLQ-MY24 MM modules and FACT/GOG and FACIT surveys of neurotoxicity and fatigue, respectively. The EORTC QLQ-C30 incorporates nine multi-item scales including five functional scales, three symptom scales and a global health and quality of life scale. It is a reliable and valid measure of QOL in cancer patients and takes about 11 minutes to administer. The EORTC has also developed a module specific for MM (EORTC QLQ-MY24) to be used in conjunction with the C30 scale. This scale is designed to evaluate the effect of the disease and drug therapy in patients with myeloma. The instrument consists of a brief questionnaire that has been validated and utilized in many countries. The two symptom specific subscales, the FACT/GOG-NTX (neurotoxicity) and FACIT-F (fatigue), will be utilized in this study to evaluate their sensitivity to anticipated side effects of PS-341. The neurotoxicity subscale consists of 11 symptoms. The fatigue subscale has 13 items and has been validated against Eastern Cooperative Oncology Group (ECOG) performance status in an oncology population. For both scales, patients are asked to respond on a five-point Likert scale.

Reviewer comment: QOL endpoints in single arm studies are not acceptable for registration.

3.12. Amendments to protocol

Amendment 1: 15 December 2000

- Lowered the PS-341 dose from 1.5 mg/m ^{2} to 1.3 mg/m ^{2} and explain the rationale for the lower dose. The PS-341 dose of 1.3 mg/m^2 was selected because this dose

was determined to be the maximally tolerated dose in a Phase I study of PS-341 utilizing the same treatment schedule [a three-week treatment cycle consisting of four PS-341 doses (on Days 1, 4, 8, and 11) followed by a 10-day rest period].

Amendment 2: 2 April 2001

- Required pharmacokinetic analyses to be performed only for patients participating in this study at the Dana Farber Cancer Institute, Boston, MA.

Amendment 3: 21 June 2001

- Revise the inclusion criterion regarding required Baseline (i.e., before study drug administration on Day 1, Cycle 1) hematologic values in order to better match the hematologic values generally seen among patients with refractory MM.

Amendment 4: 17 July 2001

- Allowed for the enrollment of up to 75 additional patients in the study, making the *maximum* number of patients to be enrolled in the study 150 rather than 75.

Amendment 5: 31 July 2001

- Allowed patients who experience progressive disease (PD) after completing the first two treatment cycles (Cycles 1 and 2) to receive PS-341 1.3 mg/m^2/dose plus dexamethasone 40 mg in the subsequent two treatment cycles (Cycles 3 and 4) rather than requiring that such patients be discontinued from the study.

Amendment 6: 12 October 2001

- Revised the inclusion criterion to consider patients with non-measurable MM (i.e., patients with nonsecretory or oligosecretory MM) eligible for enrollment in the study. The investigator is to contact the medical monitor before a patient with non-measurable disease may be enrolled in the study.

  Patients with non-measurable disease at the time of enrollment will be excluded from all statistical analyses of disease response using Southwestern Oncology Group (SWOG) criteria. Such patients will be presented in a descriptive fashion in the clinical study report.

- Clarify that the investigator may consider patients with a creatinine clearance >10 mL/minute and <30 mL/minute due to significant myelomatous involvement of the kidneys eligible for study enrollment on a per-patient basis after consultation with the medical monitor.

- Clarify that kyphoplasty is not considered to be a major surgery requiring exclusion from or delay of enrollment in the study.

- Prohibit concomitant radiation therapy. If localized radiation therapy is, in the investigator's opinion, necessary for the treatment of cancer complications, then such therapy must be discussed in advance with the medical monitor. Furthermore, receipt of localized radiation therapy will not require a delay in enrollment in the study.

- Increase the total number of patients to be enrolled in the study from up to 150 to 200.

4 Study protocol No M34100-024

A Randomized, Open-Label, Phase II Study of Two Doses of PS-341 Alone or in Combination with Dexamethasone in Patients with Multiple Myeloma Who Have Failed to Respond to or Relapsed Following Front-line Therapy

This study was submitted to provide supportive efficacy and additional safety data for the study 025. The study objectives and entry criteria were similar to study 025, with the exception that patients were eligible who had received a single course of therapy, and two different doses of PS-341 were studied. Only the differences between this protocol and 025 will be emphasized below.

4.1. Study design

Study 024 was a prospective, randomized, open-label, multicenter study designed to evaluate the efficacy and safety of two dose levels of PS-341 (1.0 and 1.3 mg/m^2/dose) administered in up to eight treatment cycles. A treatment cycle is comprised of four injections of PS-341 (on Days 1, 4, 8, and 11) followed by a 10-day rest period. Eligible patients had a diagnosis of MM who had failed to respond to or relapsed following front-line therapy, either conventional therapy (e.g., VAD or MP) or high-dose therapy.

4.1.1 Primary Objective:

- To determine the response rate [the combined complete response (CR) + partial response (PR) + minimal response (MR)] following treatment with PS-341 1.0 or 1.3 mg/m^2/dose monotherapy in patients with MM.

4.1.2 Secondary objectives

- To determine the response rate (CR + PR + MR) following treatment with combination therapy with PS-341 (1.0 or 1.3 mg/m^2/dose) plus dexamethasone 40 mg in patients with MM who failed to respond or relapsed after treatment with PS-341 alone.
- To assess the safety and tolerability of two dose levels of PS-341 (1.0 and 1.3 mg/m^2/dose) alone and in combination with dexamethasone in patients with MM.

4.1.3 Entry criteria

Patients were eligible who had received previous front-line therapy (including high-dose therapy with stem cell support) and had documentation of relapse/failure to that therapy (ie, failed to achieve a CR, remission or PR to front-line therapy, progression during front-line therapy or relapse at any time after completing front-line therapy).

Reviewer comment: These patients were relapsed but were not considered to be truly refractory by the FDA reviewer, although "refractory" may be difficult to define in this disease, which commonly relapses and then may respond to multiple cycles of therapy.

4.2. Treatment plan

Patients received a maximum of eight cycles of study drug. During the ~~first~~ two study drug cycles (Cycles 1 and 2), all patients received PS-341 alone at the dose to which they were randomized. Subsequently, treatment was modified according to the patient's response to the previous therapy. Patients were evaluated after Cycles 2, 4, and 6 to determine what treatment will be administered during the following two cycles

Patients who experience PD after Cycles 1 and 2 or PD or NC after Cycles 3 and 4 were to start treatment with PS-341 at the same dose plus dexamethasone 20 mg PO four times a week. After completion of Cycle 4, patients who are receiving PS-341 plus dexamethasone and experience PD are to be discontinued from the study. Dose modification and concomitant medication rules were similar to 025.

4.2.1 Patient allocation to dose groups

Patients were randomized in a 1:1 ratio into two treatment groups: one group received 1.0 mg/m^2/dose and the other group received 1.3 mg/m^2/dose. Table 1 summarizes the patient allocation, which was designed to provide a balanced allocation of 64 patients according to prior therapy and prognosis.

Table 7: Treatment/ group planned assignment for study 024

		Number of Patients		Total
Stage	Prior Therapy	1.0 mg/m^2/dose	1.3 mg/m^2/dose	Patients
I-II	Conventional[a]	8	8	16
	High dose[b]	8	8	16
III	Conventional[a]	8	8	16
	High dose[b]	8	8	16

[a]Conventional-dose therapy: MP or VAD.
[b]High-dose therapy: high-dose melphalan and dose intensive regimens requiring mobilized peripheral blood stem cell support.

4.2.2 Efficacy and safety evaluations:

Efficacy and safety evaluations are similar to those in study 025. An independent response committee assessed patients for response as in study 025. Response criteria, and assessment schedules were identical between the two studies. Safety reporting requirements were identical to study 025. Efficacy results were to be analyzed by descriptive statistics.

4.3. Amendments to protocol 024

Amendment 1: 30 March 2001

- Require pharmacokinetic analyses to be performed for patients participating in this study at the Dana Farber Cancer Institute, Boston, MA.

Amendment 2: 8 June 2001

- Administrative changes
- Revise the inclusion criterion regarding required baseline lab values if the bone marrow is extensively infiltrated.

Amendment 3: 3 August 2001

- Add determination of bone resorption (turnover) markers, Add blood sample collection for population pharmacokinetics Require that an additional blood sample for the 20S proteasome inhibition assay.

Amendment 4 12 October 2001

- Revise the inclusion criterion to consider patients with non-measurable MM (i.e., patients with nonsecretory or oligosecretory MM) eligible for enrollment in the study.
- Revise the inclusion criterion to allow a minimum absolute neutrophil count (ANC) of 0.5 × 109/L (rather than 1.0 × 109/L) if due to significant marrow infiltration and not an unresolved toxicity of previous chemotherapy.
- Clarify that the investigator may consider patients with a creatinine clearance >10 mL/minute and <30 mL/minute due to significant myelomatous involvement of the kidneys eligible for study enrollment on a per-patient basis after consultation with the medical monitor.
- Clarify that kyphoplasty is not considered to be a major surgery requiring exclusion from the study or delay in enrollment in the study.

Amendment 5: 31 January 2002

- Require that patients who have not experienced progressive disease confirmed (PD) on their most recent study drug regimen, whether PS- 341 alone or PS-341 plus dexamethasone, by the End of Study visit to attend follow-up visits on an every six-week basis for disease response and quality of life (QOL) assessments and directed neurotoxicity questioning until development of confirmed PD.
- Revise the planned statistical methods to include an analysis of the rates of complete response.

5 Study Results: Population

5.1. Study Population: 024 and 025

Study populations for the two studies 024 and 025 will be analyzed together, and efficacy results for the two studies 024 and 025 will be analyzed separately.

5.1.1 Patient Demographics

The majority of the 256 patients treated in study 024 and 025 were male (144 patients – 56%) and Caucasian (209 patients; 81%). The mean age of patients overall and within each study was 60 years with a range of 34 to 84 years. Baseline Karnofsky performance status score was determined to be 70 for patients with data available Table 4 presents the demographic characteristics of the study populations on 025 and 024. Demographic characteristics are summarized in Table 8:

Table 8: Demographic Characteristics (All Patients; Studies M34100-025 and M34100-024)

	Study M34100-025 (1.3 mg/m^2) by Cohort and Overall			Study M34100-024 by Dose Group and Overall		
	Cohort 1	Cohort 2	Total	1.0 mg/m^2	1.3 mg/m^2	Total
Characteristic / Statistic	(n=78)	(n=124)	(n=202)	(n = 28)	(n = 26)	(n = 54)
Sex [N, (%)]						
N	78	124	202	28	26	54
Male	46 (59)	75 (60)	121 (60)	14 (50)	9 (35)	23 (43)
Female	32 (41)	49 (40)	81 (40)	14 (50)	17 (65)	31 (57)
Race [N (%)]						
N	78	124	202	28	26	54
White	62 (79)	102 (82)	164 (81)	25 (89)	20 (77)	45 (83)
Black	8 (10)	13 (10)	21 (10)	3 (11)	3 (12)	6 (11)
Asian	5 (6)	0 (0)	5 (2)	0	2 (8)	2 (4)
Other	3 (4)	9 (7)	12 (6)	0	1 (4)	1 (2)
Age (years)						
N	78	124	202	28	26	54
Mean (±SD)	60 (9.5)	60 (9.2)	60 (9.3)	64 (11.7)	60 (12.2)	62 (12.0)
Median	59	59	59	65	61	63
Minimum, Maximum	39, 84	34, 83	34, 84	39, 82	30, 84	30, 84
KPS [N (%)]						
N	76	120	196	28	26	54
60	9 (12)	10 (8)	19 (10)	2 (7)	2 (8)	4 (7)
70	10 (13)	11 (9)	21 (11)	1 (4)	2 (8)	3 (6)
80	34 (45)	40 (33)	74 (38)	8 (29)	8 (31)	16 (30)
90 or 100	23 (30)	59 (49)	82 (42)	17 (61)	14 (54)	31 (57)
Creatinine clearance (mL/min)						
N	78	123	201	28	26	54
Mean	83.8	77.7	80.0	72.3	88.8	80.2
SD	34.43	35.31	35.01	31.10	40.12	36.35
Median	79.6	70.4	73.9	71.2	81.8	74.5
Minimum, maximum	28.6, 220.9	13.8, 180 5	13.8, 220.9	22.9, 130.8	37.4, 183 4	22.9, 183.4

KPS (Karnofsky performance score)

5.1.2 Disease characteristics

These 2 studies accrued 256 patients who had been previously diagnosed with MM based on standard criteria. These patients had evidence of relapse following a response to standard first-line chemotherapy (e.g., VAD or MP) or first-line high-dose chemotherapy, and were refractory (i.e., failure to achieve at least CR, PR, or stable disease) to their most recent chemotherapy, whether or not containing systemic corticosteroids. Patients with Wadenstrom's macroglobulinnemia (IgM) were excluded. Specific types of myeloma including type of myeloma protein secreted are summarized in Table 9 below:

Table 9: Type and Duration of Multiple Myeloma

Study	024	025
Characteristic Type of myeloma	(N = 54) [N, (%)]	(n=202) [N, (%)]
IgG	32 (59)	122 (60)
Kappa	23 (43)	86 (43)
Lambda	9 (17)	36 (18)
IgA	14 (26)	48 (24)
Kappa	11 (20)	30 (15)
Lambda	3 (6)	17 (8)
Kappa + Lambda	7 (13)	1 (<1)
IgD lambda		2 (<1)
IgM lambda		1 (<1)
Light chain	1 (2)	28 (14)
Unspecified		1 (<1)
oligo- or non-secretory myeloma	6 (11)	19 (9)

Cytogenetic abnormalities, particularly deletion and other abnormalities of chromosome 13 are correlated with adverse prognosis. Table 10 summarizes the cytogenetic findings in the patients enrolled in the two studies:

Table 10: Cytogenetic findings

Study	025	024
Characteristic	(n=202)	(n = 54)
Karyotype normal [n (%)]	108 (63%)	28 (51%)
Karyotype abnormal [n (%)]	60 (35%)	18 /47 (38%)
Unevaluable/Missing [n (%)]	4 (2%)	8 (15%)
Chromosome 13 Deletion [n/N (%)][c]	26/172 (15%)	5/18 (28)

A summary of prior therapies for myeloma in patients entered into the two trials is summarized in Table 11 below:

Table 11: Prior Therapy for Multiple Myeloma (N = 256)

STUDY	024		025
PS-341 Dose Group	1.0 mg/m^2	1.3 mg/m^2	1.3 mg/m^2
Therapy	(n = 28)	(n = 26)	(n=202)
Any Prior Steroids, eg, dexamethasone, VAD [N (%)]	27 (96)	26 (100)	201 (>99)
Any Prior Alkylating Agents, eg, MP, VBMCP [N (%)]	21 (75)	18 (69)	186 (92)
Any Prior Anthracyclines, eg, VAD, mitoxantrone [N (%)]	12 (43)	17 (65)	163 (81)
Any Prior Thalidomide Therapy [N (%)]	9 (32)	7 (27)	168 (83)
Received at Least 3 of the Above[a]	14 (50)	14 (54)	185 (92)
Received All 4 of the Above[a]	2 (7)	4 (15)	134 (66)
Any Prior Stem Cell Transplant /Other High-dose Therapy [N	15 (54)	11 (42)	129 (64)
Prior Experimental or Other Types of Therapy [N (%)]	3 (11)	3 (12)	89 (44)
Any Prior Radiation Therapy [N (%)]	10 (36)	8 (31)	
Number of Prior Regimens[b] of Treatment			
Mean ± SD	3 ± 1.8	3 ± 1.6	6 (2.8)
Median	3	3	6
Minimum, Maximum	1, 7	1, 7	2, 17

The majority (>96%) of all patients had received prior therapy with corticosteroids, e.g., dexamethasone alone or in the VAD combination (vincristine, Adriamycin, dexamethasone). A total of 225 (87%) of all 256 patients had received prior treatment with alkylating agent therapy, e.g., melphalan alone or in combination with prednisone. Approximately 75% of all patients had received prior therapy with anthracyclines, a higher proportion in study 025. Although not approved for the treatment of MM, 70% of all patients had received prior therapy with thalidomide including 30% of patients in study 024 and 83% in study 025. the 1.3 mg/m^2 dose group. Forty eight percent of all patients in study 024 and 64% of patients in study 025 had received prior high-dose therapy with stem cell transplant. In general, the patients in study 025 appeared to have been more heavily pre treated compared with those in study 024. The mean duration since diagnosis was 3.1 years in study 024 and 4.5 years in study 025.

Entry criteria for study 024 required relapse following "first-line therapy," and patients in study 025 were eligible who had received at least 2 prior regiments. The study populations had a mean of 6 and range of 2-17 prior regimens in study 025 and a mean of 3.17 and range of 1-10 prior therapies in study 024. See Table 12 below for a summary of number of prior regimens for the two studies:

Table 12 Number of Prior Regimens (#R's) vs number of patients

Number of prior Regimens	1	2	3	4	5	6	7	8	9	10	11	12	13	≥14
Study 025	0	11	16	35	28	34	22	21	10	9	3	2	5	6
Study 024	13	7	19	8	3	2	4		1					

Source: Datasets PRIORTHER

Reviewer comment: FDA identified 5 patients in study 025 who had received only clarithromycin (biaxin) or thalidomide and corticosteroids. Although these patients were technically eligible for enrollment in the studies, these patients were not considered to have had two prior therapies and were therefore excluded from the FDA analysis population (see table 13). Five additional patients were identified in study 024 who had received only corticosteroids.

Table 13: Minimally Pretreated Patients (excluded from FDA efficacy analyses)

Study	Dose	Patient ID	Response	Prior Therapy
024	1.3	003001	PD	Dexamethasone
	1.0	003003	PR	Dexamethasone
	1.3	003006	PR	Dexamethasone
	1.0	003007	PR	Dexamethasone
	1.3	009004	PD	Dexamethasone
025	1.3	003003	PD	Dexamethasone, Biaxin
	1.3	003007	PD	Dexamethasone, Biaxin
	1.3	003025	PD	Dexamethasone + Biaxin
	1.3	003032	PD	Dexamethasone + Thalidomide
	1.3	003033	CR (Blade)	Dexamethasone + Biaxin

Source: Datasets PRIORTHER

5.1.3 Analysis populations

Data from 202 patients enrolled and treated in this study are included in safety analyses. Primary efficacy analyses were conducted on the ITT population. The study protocol (by amendment) allowed for patients with non-measurable disease (i.e., oligo- and non-secretory MM) to be enrolled. These patients were excluded by the sponsor from efficacy analysis. The FDA excluded an additional 3 patients who were only treated with corticosteroids and biaxin.

Table 14: Populations for Analysis

Population n (%)	Study 025	Study 024
All Treated Patients	202 (100%)	54 (100%)
Sponsor efficacy ITT Population	193 (96%)	53 (98%)
FDA efficacy population	188 (93%)	48 (89%)

5.2. Conclusions

Study 025 was a hetrerogenous group which included 3 patients who had received only corticosteroids and biaxin as well as 63 patients who had received multiple stem cell transplants and other therapies. Study 024 was in general less heavily pretreated and included 5 patients who had received only corticosteroids. The relatively lightly pretreated patients were excluded from the FDA efficacy analysis for the refractory indication. If the relatively lightly treated patients are excluded, then the study populations from study 025 and 024 could support the proposed indication of relapsed and refractory myeloma.

6 Study conduct: 024 and 025

6.1. Protocol Deviations and violations

The following Table summarizes study protocol deviations and violations for studies 024 and 025:

Table 15: Inclusion and Exclusion Criteria Violations

Study 025	Number (%) of Patients	Patient ID
Hemoglobin <8.0 g/dL	5/202 (2%)	02-0008, 03-0022, 12-0001, 12-0021
Platelet count <30× 10^9/L	4/202 (2%)	03-0027, 08-0002, 05-0010, 11-0007, 14-0008,17-0003
ANC <0.5× 10^9/L	1/202 (<1%)	17-0003
Non-measurable Disease	1/202 (<1%)	02-0016
Receipt of chemotherapy within 3 wks of enrollment	5/202 (2%)	03-0031, 12-0014, 12-0016, 12-0019, 12-0022
Receipt of corticosteroids within 3 wks of enrollment	8/202 (4%)	02-0020, 02-0030, 03-0027, 05-0004, 06-0022, 14-0009

Study 024			
	Patients	Patient ID	Dose Group
Receipt of chemotherapy within 3 wks of enrollment	1 (2%)	002-0009	1.3 mg/m^2
Received more than front-line therapy	3 (6%)	002-0001	1.0 mg/m^2
		002-0006	1.0 mg/m^2
		006-0004	1.0 mg/m^2

Source: sponsor study reports

Protocol deviations were fairly minor. Deviations from the dosing regimen were observed in several patients. One patient was scheduled to receive, and received 1.0 mg/m^2 as the initial dosing regimen instead of the protocol-planned 1.3 mg/m^2. Patient 12-0021, who was a [redacted], entered the study with a hemoglobin of 5.4 g/dL. Based on the patient's compromised status, the patient received both sponsor and IRB approval to enter the study and to receive a lower starting dose of PS-341. In addition, 4 patients at Site 02 scheduled to receive 1.3 mg/m^2 received ~1.0 mg/m^2 due to an error in determination of body surface area (Patient Nos. 02-0004, 02-0009, 02-0012, and 02-0021).

6.2. Study Discontinuations and Patient Disposition

Table 16 summarizes the reasons for study discontinuation in the trials and by dose, and a narrative account of patients who discontinued from the study after receiving two or fewer doses follows the table:

Table 16: Study Discontinuations

Study	024		025
N	28	26	202
Dose (mg/m^2)	1.0	1.3	1.3
Completed Study	18	11	80 (40%)
Reason for Discontinuation			
Lack of Efficacy	4	7	54 (27%)
Patient Request	1	1	8
Adverse event	3	9	45 (22%)
Added Dexamethasone			78
Intercurrent Illness			4
Non Compliance/administrative		1	10

Source: Datasets

One patient in study 24, 014004, never received the scheduled dose of 1.3 mg/m2 and instead received a lower dose of 1.0 mg/m2 and was subsequently discontinued and died 31 days after receiving the dose. Three patients in study 025 discontinued after only one dose. Patient 002023 was hospitalized 2 days after the first dose with hyperviscosity and altered mental status, and died 13 days after the single dose was administered. The cause of death was progressive disease. An autopsy report indicated acute mental status changes progressing to coma, respiratory failure, and acute renal failure without identifying an etiology for these findings. Patient 003014 was discontinued off study after experiencing an arterial embolus on the evening after receiving her first dose. Patient 012014 was enrolled in the study with spinal cord compression present at baseline. The patient was withdrawn from the study after receiving a single dose of PS-341 due to lack of efficacy. Two patients in study 025 discontinued after only two doses. Patient 002024 was discontinued after 2 doses due to exacerbation of back pain attributed to progressive disease. Patient 003018 was discontinued subsequent to the second dose after experiencing abdominal distension attributed to ascites, dehydration, and diarrhea, and died 12 days after the first dose of study drug. The death was listed as cardiopulmonary arrest secondary to disease progression.

The FDA analysis of dose modifications is summarized in the Table below:

Table 17: Dose Modifications

Study	024 (1.0 mg/m2)	024 (1.3 mg/m2)	025 (1.3 mg/m2)
Doses held	2.5%	5%	10%
Doses reduced	8.5%	68%	31%
Assigned dose given*	63%	24%	57%
Doses increased	25%	3%	1%

* 0.95-1.05 mg/m^2 in the 1.0 dose group, and 1.20- 1.35 mg/m^2 in the 1.3 mg/m^2 dose group.

PS-341 appeared to be better tolerated at a dose of 1.0 mg/m2 than a dose of 1.3 mg/m^2.

6.3. Conclusions

The studies were generally well conducted and protocol violations were minor. Thirty nine percent of all 230 patients in both studies on the 1.3mg/m^2 dose completed the study, while 67% of patients on the 1.0 mg/m^2 dose in study 024 were able to complete the study (p=.0057). Twenty three percent of 230 patients receiving the 1.3 mg/m^2 dose discontinued the drug because of an adverse event compared with 11% of patients on the 1.0 mg/m^2 dose (p=.2). An approximately equal number of patients discontinued the study for lack of efficacy on either dose. PS-341 appeared to be better tolerated at a dose of 1.0 mg/m^2 than a dose of 1.3 mg/m^2. Forty percent of all doses were held or decreased in study 025 and over half of all doses were held or decreased at the 1.3 mg/m2 dosing group in study 024. Several patients discontinued the study drug after only one or two doses, the cause was generally attributed to progressive disease.

7 Study 025 Efficacy Results

Efficacy results for study 025 were reviewed in detail.

7.1. Primary Efficacy Endpoint: Response Rate

The primary efficacy endpoint was response rate, according to a variety of response criteria (see introduction). The criteria for each response analysis are described in detail in the previous section of the NDA review on primary efficacy analysis. CR (IF+) was an exploratory response analysis which has not been validated as a clinical benefit: it is not clear that CR(IF+) patients have improved survival. SWOG response criteria have been used for many years to evaluate responses in MM. All CR (Blade) and CR (IF) and SWOG Clinical Responses were verified by the FDA using datasets and patient data listings and by reviewing the IRC worksheets and notes. Table 5 summarizes the FDA and sponsor's efficacy results of the study 025 for patients treated with PS-341 alone.

Table 18: Efficacy Results of Study M34100-025

Response Analyses (VELCADE monotherapy)	Sponsor N=193			FDA* 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.
*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}

The differences in response rates by CR (Blade) criteria between the FDA and sponsor are due to the exclusion of one patient who was minimally pretreated, and from a patient whose complete response could not be confirmed. FDA was unable to confirm one of the CR (Blade)'s because of lack of confirmatory IF data. Of the 6 confirmed CR(Blade) responders, two occurred in heavily pretreated patients. One of these patients had undergone multiple cycles of chemotherapy including 3 stem cell transplants, thalidomide, and multiple courses of corticosteroids and in addition had a deletion of chromosome 13, an adverse prognostic indicator. The other patient had undergone stem cell transplant and multiple additional prior therapies (Table 19):

Table 19: CR(Blade) Heavily pretreated patients

PAT # 002015	PAT # 003001
Treatments received:	**Treatments received:**
VMCP	DECADRON
DEX PULSING #VAD	BUSULFAN #CYTOXAN #PSCT
CDEP	PREDNISONE
MELPHALAN / PBSCT	DECADRON
MELPHALAN / PBSCT	THALIDOMIDE
PBSCT	DECADRON
DEX PULSING	ADRIAMYCIN #DEXAMETHASONE #VINCRISTINE
THALIDOMIDE	PREDNISONE
IDIOTYPE VACCINE #INTERFERON	BIAXIN
DEX PULSING	MELPHALAN
IM'D (THALIDOMIDE)	

The prior therapies of 5 additional patients who were included in the sponsor's CR(Blade) dataset are summarized in the table below:

Table 20: Additional CR (Blade) patients: Prior Therapy

PAT #	Treatments received.
003021	MELPHALAN #PREDNISONE
	VAD
003033 [a]	DECADRON
	PREDNISONE
	BIAXIN
006002	VAD
	MEPHALAN
	THALIDAMIDE
	DCEP
	DEXAMETHASONE PULSE
014015	VAD
	CYTOXAN / DECADRON
	MELPHALAN + HOLMIUM166 - DOTMP
	BIAXIN/ADRIAMYCIN/DECADRON
012027 [b]	ADRIAMYCIN #DEXAMETHASONE #VINCRISTINE
	PERIPH AUTOLOG STEMCELL TRANSPLANT
	THALIDOMIDE
	DEXAMETHASONE

[a] Patient excluded from FDA efficacy analysis

[b] CR (Blade) not confirmed by FDA

These patients had been were moderately pretreated. One of the patients, 003033, was excluded from the FDA efficacy analysis because this patient had only been treated with corticosteriods, and although this patient fit the criteria for inclusion in study 025, and the CR(Blade) was confirmed by the FDA, this response could not support the proposed indication of refractory myeloma,. An additional patient could not be confirmed as a CR (Blade). Therefore the population achieving a CR(Blade) which could support the proposed indication of relapsed and refractory Myeloma, consisted of a somewhat heterogenous population of 2 heavily pretreated patients and 3 moderately pretreated patients.

7.1.1 Time to Response

The sponsor's summary of time to response is shown below:

Table 21:Sponsor's Summary of Time to Response on PS-341 Alone (Days) (CR, PR or MR Patients, N = 67)

Response Category	N	Median	Minimum[a]	Maximum
CR+PR	53	38	30	127
CR	19	36	35	47
CR^{Blade}	7	36	35	47
CR^{IF+}	12	36	35	42
PR	34	42	30	127
CR^{SWOG}	34	36	30	84
MR	14	38	31	155

[a] The first evaluation was conducted in the rest period of Cycle 2 beginning Day 33.

Most responses occurred on the first or second cycle, but occasional late responses did occur.

7.1.2 Duration of Response

Duration of response was defined as the time from the date of first evidence of confirmed response to the date of disease progression. The sponsor's summary of duration of response is shown in the table below.

Table 22: Sponsor's Duration of Response on PS-341 Alone by Response Category

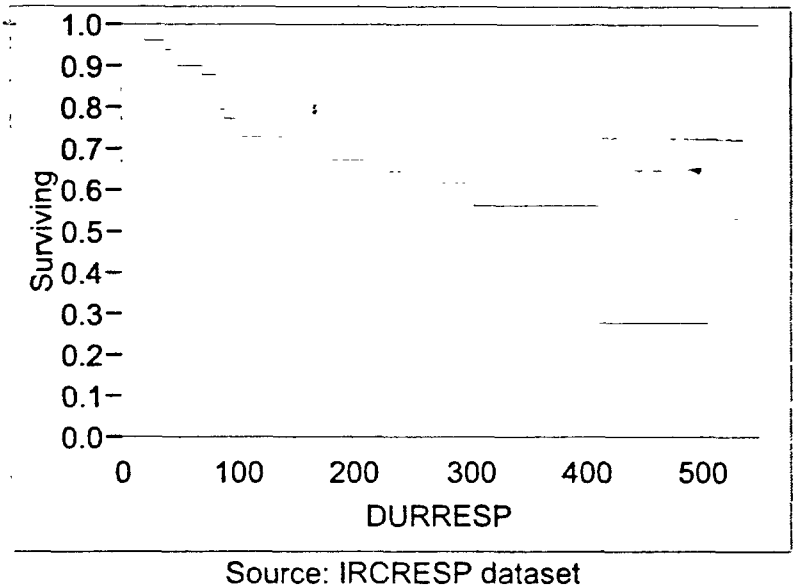
Response Category	N	Median	% Censored	Minimum	Maximum
CR+PR	53	365	70	41+	509+
CR	19	365	74	43	509+
CR^{Blade}	7	??	86	61+	463
CR^{IF+}	12	365	67	43	509+
PR	34	245	68	41+	369+
CR^{SWOG}	34	463	76	42+	509+
MR	14	136	71	41+	483+

Note: + denotes censored value;

The study duration of 025 was 24 weeks or 168 days. The sponsor provided information from the extension studies and the FDA was therefore able to confirm a median time of CR+PR duration of 142 days, and a Kaplan-Meier estimate of median duration of CR+PR of 365 days.

The CR (Blade) responders were followed for a median of 107 days, minimum of 52, maximum of 156 days,and none of these patients relapsed. The CR (IF) patients were followed for a median of 96 days prior to relapse or censoring on study 025. In these 12 patients, 5 patients progressed, and the median duration of response was 154 days. The analysis of response duration, which included data from the extension studies, showed an overall Kaplan-Meier estimate of median of duration of CR+PR of 365 days. The FDA duration of CR+PR, based on an analysis of IRC response data, including data provided from the extension studies, is shown in Figure 2 below:

Figure 2: FDA Duration of CR+PR



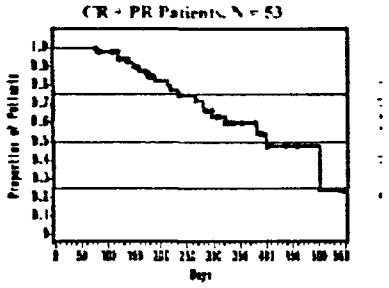
Source: IRCRESP dataset

Nineteen patients relapsed and 34 patients were censored, and the median duration of response was 365 days in this analysis.

7.1.3 Time to Progression

The sponsor performed such an analysis using data from the extension study 029. The sponsor estimated that the median time to progression was 218 days. The sponsor's Kaplan-meier time to progression graph is shown in Figure 3 below:

Figure 3: Sponsor's Kaplan-Meier Time to Progression Curve for PS-341 alone



7.1.4 Response in Various Subgroups

In order to define the group of patients who may benefit from treatment with VELCADE, a number of subgroup efficacy analyses were performed. The sponsor's analysis of response to treatment (CR + PR) with PS-341 alone by baseline demographic characteristics is presented in the following Table:

Table 23: Subgroup Analysis of Response to Treatment with PS-341 Alone

ITT Population, N = 193		
Characteristic	**CR or PR Rate**	**p-value[a]**
Age (years)	**n/N (%)**	
<65 (N = 124)	40/124 (32)	0.064
65 (N = 69)	13/69 (19)	
Sex	**n/N (%)**	
Male (N = 118)	31/118 (26)	0.741
Female (N = 75)	22/75 (29)	
Race	**n/N (%)**	
White (N = 157)	38/157 (24)	0.064
Black (N = 21)	10/21 (48)	
Other (N = 15)	5/15 (33)	
BSA (m^2)	**n/N (%)**	
2 (N = 123)	31/123 (25)	0.403
> 2 (N = 70)	22/70 (31)	
Karnofsky Performance Status	**n/N (%)**	
70 (N = 34)	12/34 (35)	0.524
80 (N = 74)	20/74 (27)	
90 (N = 80)	20/80 (25)	

Source: Sponsor's Report [a]Two-sided Fisher's exact test.

A 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%). The number of Black patients and patients of other races was small relative to the study population.

The sponsor's analysis of response to treatment (CR + PR) in different subtypes of MM is summarized in the following Table:

Table 24 Subgroup Analysis of Response to Treatment with PS-341 Alone by Baseline Disease Characteristics (ITT Population, N = 193)

Characteristic	CR or PR Rate n/N (%)	p-value[a]
Myeloma Type		
Heavy chain (N = 166)	44/166 (27)	0.489
Light chain (N = 27)	9/27 (33)	
Myeloma Type		
IgG (N = 116)	28/116 (24)	0.414
IgA (N = 47)	15/47 (32)	
Light chain (N = 27)	9/27 (33)	
Bone Marrow Biopsy		
Plasma Cells >50% (N = 85)	17/85 (20)	0.030
Plasma Cells ≤ 50% (N = 93)	33/93 (35)	
Cytogenetics		
Abnormal (N = 57)	11/57 (19)	0.047
Normal (N = 105)	37/105 (35)	
Chromosome 13 Deletion		
Yes (N = 25)	6/25 (24)	0.812
No (N = 168)	47/168 (28)	
Hemoglobin		
<10.5 g/dL (N = 105)	24/105 (23)	0.145
10.5 g/dL (N = 88)	29/88 (33)	

Source: Sponsor's report [a] Two-sided Fisher's exact test.

Response to PS-341 alone was similar in the different subtypes of myeloma, i.e., heavy chain including IgG and IgA and light chain disease. Patients with >50% plasma cells at the screening bone marrow assessment had a lower response rate (20%) compared to those patients with ≤ 50% plasma cells in the bone marrow (35%; p = 0.030). Patients with abnormal cytogenetics had a lower response rate (19%) compared to those patients with normal marrow cytogenetics at screening (35% p = 0.047), however there was no observed difference in response rate for patients with chromosome 13 abnormalities (24%) compared to those without abnormalities (28%).

The Sponsor's analysis of response (CR + PR) to PS-341 by number and type of prior therapies is summarized in the following Table:

Table 25: Response to PS-341 Alone by Prior Therapies (ITT Population, N = 193)

Prior Therapy	CR + PR Rate [n/N (%)]
Any Prior Steroids, e.g., dexamethasone, VAD	53/192 (28)
Any Prior Alkylating Agents, e.g., MP, VBMCP	48/177 (27)
Any Prior Anthracyclines, e.g., VAD, mitoxantrone	46/154 (30)
Any Prior Thalidomide Therapy	45/159 (28)
Received at Least 2 of the Above[a]	52/189 (28)
Received at Least 3 of the Above[a]	50/176 (28)
Received All 4 of the Above[a]	37/125 (30)
Any Prior Stem Cell Transplant /Other High-dose Rx	36/122 (30)
Prior Experimental or Other Types of Therapy	25/87 (29)
Number of Prior Therapeutic Regimens	
2 to 3 Prior Regimens	10/31 (32)
4 to 6 Prior Regimens	22/95 (23)
7 Prior Regimens	21/67 (31)

a Received 2, 3 or 4 of the following: dexamethasone, alkylating agents, anthracyclines, or thalidomide. b As reported by the investigator

There appeared to be no relationship between the response rate and the number and type of prior therapy. The FDA performed an analysis of different response endpoints in selected subgroups.

Table 26: FDA Analysis of different Response Criteria by Selected Baseline Characteristics

Subgroup	N	CR (Blade)	CR (IF)	Total SWOG RESPONSE
< 65 years of age	132	6 (4.5%)	7 (5.3%)	26 (20%)
> 65 years of age	70	0	4 (5.7%)	9 (13%)
ABNL Karyotype	67	0	3 (4.5%)	8 (12%)
B-2 macroglobulin > 3.0 mg/L	138	2 (1.4%)	5 (3.6%)	18 (13%)
S P PSCT	74	2 (2.7%)	5 (6.7%)	11 (15%)
Light Chain	27	4 (15%)	3 (11%)	10 (37%)

Source: Datasets

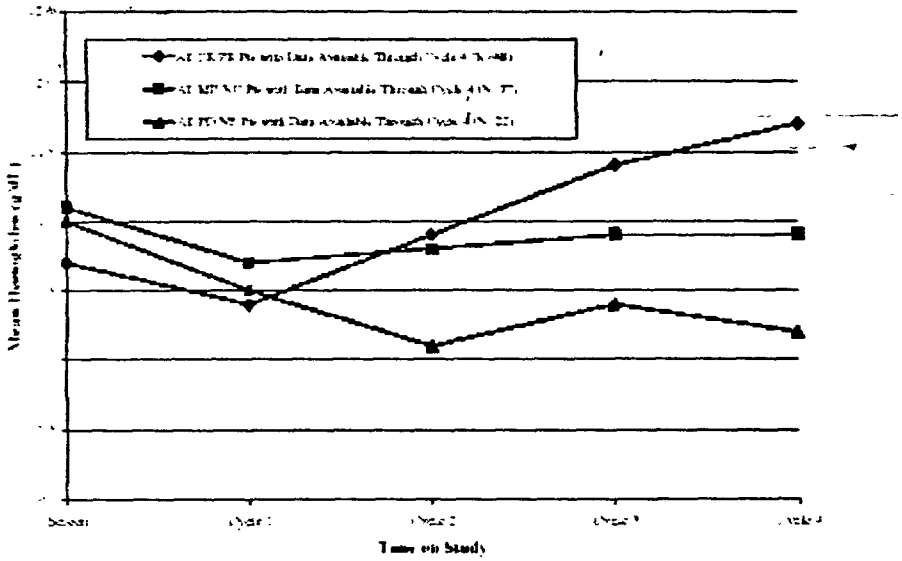
The FDA results by different response criteria were generally consistent with the sponsor's subgroup analysis of overall response. There may have been a slightly higher CR rate in the group of patients with light chain disease, and a lower rate of response in patients over 65 years of age and with abnormal cytogenetic karyotype, however the numbers are too small to reach definitive conclusions.

7.1.5 Additional clinical benefit analyses

The sponsor performed exploratory analysis of additional clinical endpoints which may benefit responding patients, including change in hemoglobin and transfusion requirements, changes in in

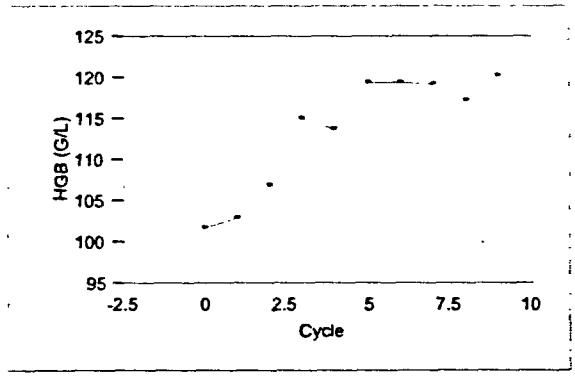
renal function, change in performance status , and changes in 'non-M protein' immunoglobulin levels. Mean hemoglobin over time for those patients who responded to treatment with PS-341 alone, i.e., those patients who were assessed by the IRC as having achieved CR or PR, along with the proportion of these patients who received red cell transfusions, is summarized in the sponsor's figure below:

Figure 4: Sponsor's Mean Hemoglobin Over Time based on response



Patients who achieved a CR or PR to treatment with PS-341 alone had an increase in hemoglobin from Cycle 1 through Cycle 4 compared with patients with NR or PD/NE. Data for subsequent cycles was insufficient for analysis. The FDA analysis showed that mean hemoglobin appeared to increase over time in 7 CR patients (Figure 3).

Figure 5: Mean Hb by cycle in CR patients (n=7)



This analysis was not controlled for transfusions or for the use of erythropoetin, although the sponsor provided narrative accounts for some patients who became transfusion independent following a response.

The sponsor observed that platelet counts also appeared to improve slightly over time on treatment for patients with a response of CR or PR to treatment with PS-341 alone. Narrative accounts described 2 responders who entered the study transfusion dependent were able to remain off platelet transfusions during the final 1 to 3 months of treatment with PS-341. Patients who achieved a CR or PR to treatment showed improved renal function through Cycle 4 as compared to those patients with MR or NC and non-responding patients who showed a decrease in renal function.

An evaluation of changes from the screening assessment for immunoglobulin levels was conducted. Mean IgM, IgA and IgG did increase from the screening assessment to the last value obtained on study for those patients who responded to treatment (CR or PR) with the mean IgM entering the normal range by the end of treatment.

Karnofsky performance status (KPS), measured on a scale of 0 to 100, was obtained at the Screening evaluation, on Day 1 and Day 11 of each treatment cycle and at the end of the study. Thirty nine (75%) of the 52 responders with data available had stable KPS (23 patients, 44%) or had an increase (16 patients, 31%) in performance status during the study. Thirteen (25%) patients had a decrease in KPS. Among those 16 patients who had an increase in performance status, 11 patients (21%) had a 10-point increase in performance status and 5 patients (10%) had a 20-point increase. Notably, 2 of the responders improved from a KPS of 60 to a KPS of 80 at the last on-study evaluation.

7.2. QOL Assessments:

The sponsor reported that patients with a response to PS-341 alone had an improvement in the EORTC-C30 Global and Physical domains and a decrease in disease symptoms, pain and fatigue. The FDA did not attempt to verify this claim, since patient reported outcomes are not interpretable on a single arm study and are therefore not acceptable for registration purposes.

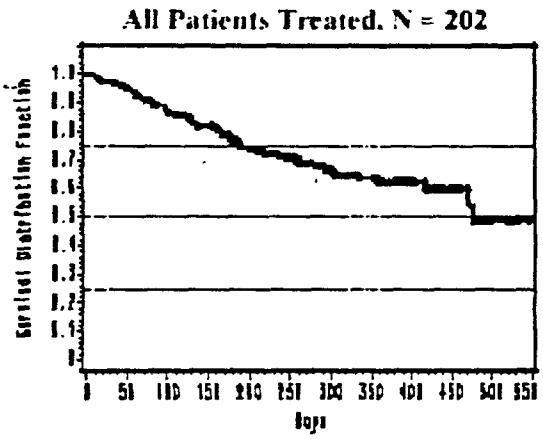
FDA statistical reviewer comments:
1) Symptom improvement is not interpretable without any control data. Symptom improvement may be confounded by concomitant medication effect and patient characteristics.
2) There is no comparative control arm (no non-Velcade arm) in the study, therefore the results are not interpretable for registration purposes.

7.3. Survival

Survival was defined as the time from the date of the first administration of PS-341 to the date of death. The sponsor's Kaplan-Meier survival curves for all patients and for the subgroups of patients based on response are presented in the figure below. Only patients known to be alive at last follow-up are censored and all available data from any follow-up, including information

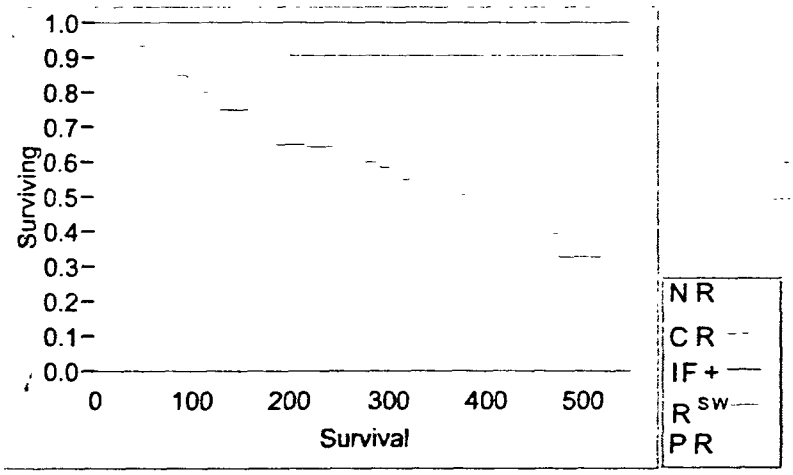
obtained on the extension study M34101-029, were utilized in the survival analysis. The FDA was not able to verify this analysis.

Figure 6:Sponsor's Kaplan-Meier survival curve for all patients treated



An exploratory analysis of survival by response category was performed, despite the methodological problems inherent with this type of analysis, the results are shown in Figure 8 below:

Figure 7: Survival by Response



NR= No response, CR=complete Response, IF+ = CR (IF), R^{SW} = Remission SWOG, PR= Partial Response

Although this type of response is flawed by potential selection of healthier patients in the better prognostic categories, it did confirm that patients with improved responses tended to live longer. Median survival for all 202 patients was reported to be around 16 months. A total of 135 (67%)

of the 202 patients were alive as of last follow-up and were censored in the analysis. It is not possible to make valid comparisons regarding survival in a single arm study design. Most reviews suggest that the median overall survival of newly diagnosed patients is around 3-4 years.

8 Study 024 Efficacy Results

The primary efficacy endpoint for study 024 was also response rate, according to the same criteria used in study 025. The criteria for each response analysis are described in detail in the section of the NDA review on primary efficacy analysis. All CR (Blade) and CR (IF) and SWOG Clinical Responses were verified by the FDA using datasets and patient data listings and by reviewing the IRC worksheets and notes. The following Table summarizes the efficacy results of the study 024 for patients treated with PS-341 alone.

Table 27: Efficacy results of Study M34100-024 (VELCADE monotherapy)

Response Analyses	1.0 mg/m^2 n = 28			1.3 mg/m^2 n = 26		
Sponsor' Analysis	N	%	95% CI	N	%	95% CI
CR^{Blade}	1	3.6%	(0, 18)	1	3.8 %	(0, 20)
CR^{IF+}	2	7.1%	(1, 24)	0	0%	(0, 13)
R^{SWOG} (includes CR^{Blade} + CR^{IF+})	4	14%	(4, 33)	4	15%	(4, 35)
CR+PR	8	29%	(13, 49)	9	35%	(20, 52)
FDA analysis*	n = 26			n = 23		
CR+PR	6	23%	(8, 35)	8	35%	(20, 53)

*FDA analysis excluded 5 less heavily pretreated patients (see previous section for discussion of response criteria)

Based on the analysis plan, the primary conclusions regarding treatment efficacy were to be based on the overall response rate (CR + PR + MR). For registration analysis, efficacy was analyzed with respect to a number of response criteria. CR^{Blade} has not yet been validated as *prima facia* evidence of clinical benefit, but durable complete remissions have been considered to evidence of clinical benefit.[1] PR's were also believed to reflect clinical benefit, but the evidence is less clear for this (see introduction). The sponsor's CR + PR rate was 29% in the 1.0 mg/m2 group compared with the 35% response rate seen in the 1.3 mg/m2 dose group. The FDA CR + PR rate was 23% in the 1.0 mg/m2 group compared with the 35% response rate seen in the 1.3 mg/m2 dose group, after exclusion of 5 less heavily pretreated patients. The 95% confidence intervals overlapped in both analyses and therefore no conclusions can be made regarding the comparative efficacy of the two doses. The numbers were too small to make conclusions regarding the comparative efficacy of the two different dose groups or for analysis of different subgroups. Eighty percent of patients were alive at one year.

9 Efficacy Conclusions

The primary efficacy endpoint was response rate, according to a variety of response criteria (see introduction). In study 025, the FDA was able to confirm 5 CR^{Blade} responses in the relapsed and refractory population for a CR^{Blade} response rate of 2.7% (95% CI 1,6). These responses were accompanied by some evidence of clinical benefit including increased hemoglobin and platelet counts, decreased transfusion requirements, and increasing physiologic immunoglobulins. The CR^{Blade} has been shown to predict for improved survival and increased time to progression in the context of transplant. CR^{Blade} responses are quite unusual in patients with relapsed and refractory myeloma unless treated with high dose chemotherapy followed by stem cell transplant. Two patients with CR (Blade) responses had been heavily pretreated with multiple prior regimens including stem cell transplant. One of these patients had a deletion of chromosome 13, considered a poor prognostic sign. The FDA analysis showed mean duration of follow-up for the CR(Blade) responders was 107 days, and none of these patients relapsed.

Additional response analyses were performed to confirm the clinical benefit of PS-341. 12 $CR^{(IF+)}$ patients achieved a 100% reduction of the serum or urine M-protein for a median of 96 days. Five (41%) of these patients relapsed and the median duration of this category of response was 96 days. A total of 30% of all patients achieved a CR or PR (50% improvement in M-protein). This partial response rate is similar to those reported in studies using thalidomide and dexamethasone and the experimental therapy CC5013 but lower than that reported in studies of relapsed and refractory patients undergoing autologous transplant. Partial responses were seen across a variety of subgroups including patients who had undergone transplant and high dose therapy, patients with elevated B-2 microglobulin, chromosome 13 deletions and elderly patients. Patients with CR^{Blade} appeared to have durable complete responses. Patients with more complete clearance of their myeloma protein appeared to have longer duration of survival than those with less complete clearance of their myeloma protein, although this analysis is methodologically flawed.

Durable complete responses may be considered to be evidence of clinical benefit.[1] The CR^{Blade} responses have not yet been validated as evidence of clinical benefit for registration in MM, however they do meet Subpart H criteria for 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. Additional clinical benefit analysis of the patients exhibiting a partial response including improved survival in these patients, further supported the clinical benefit received by these patients. Confirmation of clinical benefit may be based on an analysis of the ongoing phase 3 study 039 in MM.

VII Integrated Review of Safety

1 Brief Statement of Conclusions

The safety database is comprised of 379 patients with advanced, previously treated malignancies from six studies where VELCADE was used alone. In the four phase I studies, dose escalations were conducted with once or twice weekly IV dosing schedules for two to four weeks. The two phase II studies, with a total of 256 patients with MM, used the twice weekly times two weeks schedule. Clinical experience generally paralleled non-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.

When the results of the two phase II studies (256 patients) were combined, the most commonly reported adverse events (AEs) were: nausea (62%), fatigue (54%), diarrhea (48%), thrombocytopenia (41%), constipation (41%), pyrexia (36%), peripheral neuropathy (35%), vomiting (34%), anorexia (30%), and anemia (30%). The most common serious adverse events (SAEs) reported were pyrexia (7%), pneumonia (7%), diarrhea (5%), vomiting (5%), dehydration (5%), and nausea (4%). AEs of grade 3 severity included thrombocytopenia (13%), fatigue (5%), neutropenia (5%), diarrhea (3%), and peripheral neuropathy (3%). In total, 48% of the 256 myeloma patients experienced one or more serious adverse events.

Reviewer's comment: The frequencies of adverse events in section II: Summary of Clinical Findings refer only to the 228 patients who received the 1.3 mg/m2 dose level.

A statistical comparison of adverse events between the 1.3 mg/m2 dose and the 1.0 mg/m2 dose shows an increased frequency of diarrhea and vomiting (Fisher's exact $p < .05$) but not thrombocytopenia or SAEs at the higher dose. Increasing duration of exposure (increasing number of cycles of treatment) at the 1.3 mg/m2 dose is associated with an increasing prevalence of neuropathy ($p < .01$, anova).

Pharmacokinetic (PK) data for the proposed label dose is not yet available. Accumulation of the drug on day 11 of the 21 day cycle (dosing on day 1, 4, 8, 11) has been described when VELCADE was combined with gemcitabine, but VELCADE monotherapy PK has not been completed. Available pharmacodynamic data is limited; it does not support a dose-response or dose-toxicity relation. The database is too preliminary to describe the safety of VELCADE in special populations (hepatic or renal impairment patients) or in combination with other drugs or in pediatric patients. Hepatic and renal elimination mechanisms have been determined in animals. These have not yet been verified in humans to permit dosing guidance in patients with organ impairment. No cytochrome P450 interactions have yet been ascertained. Metabolism appears to be primarily via hepatic enzymes.

Expectant monitoring of hemodynamic, gastrointestinal (GI) and neurologic toxicity should be emphasized. The frequency and severity of diarrhea are dose dependent. At single weekly 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 website should be added to the label (http://ctep.info.nih.gov/reporting/ctc.html) to assist oncologists in the recognition and monitoring of the less common organ toxicities. The proposed vial size may pose a hazard to human use because single doses of 3.0 mg/m2 were lethal in monkeys. The

proposed single dose, non-reusable vial contains 3.5 mg of VELCADE. This could provide a 2.7 mg/m2 dose to a person whose body size is 1.5m2 or a 3.0 mg/m2 dose to a 1.2 m2 person. 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. For example, the vial label could state: do not give full contents of this vial to any person whose body size is ≤ 1.2 m2.

Safety evaluation is adequate for marketing under accelerated approval for this indication. Areas of limited safety experience have been noted above. These concerns will be 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. In addition, sponsor should provide clinicians with additional education in the recognition of and dose-adjustment for non-hematologic toxicities of anti-neoplastic drugs, such as reference to the CTC webpage in promotional materials.

2 Description of Patient Exposure

In the phase I studies of twice weekly injection, the exposure duration was modest (median 5-6 weeks) as was total dose. MTD was reached and DLTs were identified which were consistent with the non-clinical experience. Giving VELCADE twice weekly reduced the MTD compared to once per week treatment. Giving VELCADE twice weekly for four weeks also led to a reduced MTD compared to a two week exposure. In phase II, exposure averaged 20 weeks. At the 1.0 mg/m2 dose level in protocol –024, 97% of the planned dose was administered. For the 1.3 mg/m2 dose level, 85% of the planned dose was achieved for the –024 study; 85% also was achieved during the first three cycles of the –025 study. The median number of cycles in study –024 was 5 cycles. The median number of cycles for study –025 was 6 cycles.

Reviewer's Comment: For the planned dose of 1.3 mg/m2, this represents an actual administered dose intensity of 1.1 mg/m2 in studies 024 and 025 (85 percent of 1.3 mg/m2 = 1.1 mg/m2).

The following reviewer's table shows the relevant studies constituting the human experience with VELCADE at the time of the NDA filing.

Table 28: Reviewer's Summary of Safety Database

Study	Study phase	N	Dose (Mg/M^2)	Schedule	Cycle	Dose Results*	Total dose mg
DM98-194	I	53	1.45-2.0	Weekly x 4	6 weeks	MTD-1.6	22.7
98-104A	I	43	0.4-1.5	Twice weekly x 2	3 weeks	MTD-1.3	12
LCCC9834	I	27	0.4-1.38	Twice weekly x 4	6 weeks	MTD-1.04	22
M34100-027**	I	31	1.0-1.3	Twice weekly x 2	3 weeks	4.0 / 5.2	n/c
M34100-024	II	54	1.0-1.3	Twice weekly x 2	3 weeks	4.0 / 5.2	47
M34100-025	II	202	1.3	Twice weekly x 2	3 weeks	5.2	42

* mg/m2 / ** with gemcitabine / n/c not completed

Patient exposure for the phase 1 studies is included in the detailed textual description of each of these studies (vide infra). Tables of drug exposure for each of the phase 2 studies are summarized below.

In study M34100-024, 54 patients were randomly assigned to one of two treatment groups receiving PS-341 monotherapy twice weekly for two weeks each 21 days.The mean total dose of PS-341 administered in this study to all 28 patients in the 1.0 mg/m^2 group was 48.4 mg, with a range of 2.1 to 73.0 mg, and to all 26 patients in the 1.3 mg/ m^2 group the mean dose was 46.8 mg, with a range of 10.0 to 86.3 mg. The mean duration of treatment in the 1.0 mg/m2 group was 142.6 days (~5 months), with a range of 1 to 228 days (~8 months) and in the 1.3 mg/m2 group was 115.9 days (~4 months), with a range of 12 to 172 days (~6 months). The mean total PS-341 doses received were 92.2% (1.0 mg/m2 group) and 81.9% (1.3 mg/m2 group) of mean total dose expected to be administered based on number of actual cycles completed. In the 1.0 mg/m2 group, 100%, 96%, 93%, 86%, 79%, 79%, 79%, and 75% patients were treated in Cycles 1 through 8, respectively. In the 1.3 mg/m2 group, 100%, 96%, 92%, 77%, 65%, 62%, 46%, and 46% patients were treated in Cycles 1 through 8, respectively. The mean total number of PS-341 doses received was 31 (range of 1 to 32 doses) in the 1.0 mg/m2 group and 21 (range of 4 to 32 doses) in the 1.3 mg/m2 group. For both treatment groups, the mean number of doses received was similar across treatment cycles, with the mean number of PS-341 doses received ranging from 3.7 to 4.0 in the 1.0 mg/m2 group and ranging from 3.4 to 4.0 in the 1.3 mg/m2 group.

Table 29: Sponsor's Summary of Study Treatment by Cycle, Study M34100-024 (N=54)

Dose Group	Treatment Cycle							
	1	2	3	4	5	6	7	8
1.0 mg/m^2 (N = 28)	Number of patients [n (%)]:							
Treated with PS-341 in each cycle[a]	28 (100)	27 (96)	26 (93)	24 (86)	22 (79)	22 (79)	22 (79)	21 (75)
Completed each cycle[b]	27 (96)	25 (89)	26 (93)	24 (86)	21 (75)	21 (75)	21 (75)	20 (71)
At least 1 dose missed/held	1 (4)	3 (11)	0	2 (7)	3 (11)	1 (4)	2 (7)	4 (14)
At least 1 dose reduced	0	0	0	0	1 (4)	1 (4)	3 (11)	3 (11)
Received last dose of PS-341 alone in this cycle	1 (4)	6 (21)	3 (11)	5 (18)	1 (4)	4 (14)	0	8 (29)
Started dexamethasone in this cycle	0	0	5 (18)	1 (4)	5 (18)	1 (4)	4 (14)	0
Skipped a cycle	0	0	0	0	0	0	0	0
1.3 mg/m^2 (N = 26)	Number of patients [n (%)]:							
Treated with PS-341 in each cycle[a]	26 (100)	25 (96)	24 (92)	20 (77)	17 (65)	16 (62)	12 (46)	12 (46)
Completed each cycle[b]	25 (96)	21 (81)	20 (77)	19 (73)	16 (62)	13 (50)	12 (46)	9 (35)
At least 1 dose missed/held	4 (15)	5 (19)	9 (35)	7 (27)	4 (15)	6 (23)	0	3 (12)
At least 1 dose reduced	1 (4)	4 (15)	5 (19)	4 (15)	4 (15)	4 (15)	4 (15)	4 (15)
Received last dose of PS-341 alone in this cycle	2 (8)	3 (12)	3 (12)	6 (23)	2 (8)	4 (15)	1 (4)	5 (19)
Started dexamethasone in this cycle	0	1 (4)	2 (8)	0	5 (19)	2 (8)	1 (4)	1 (4)
Skipped a cycle	0	0	0	0	1 (4)	1 (4)	0	0

Source: Section 14.4, Table 14.4.1.1.

a Patients who received at least 1 PS-341 dose in the cycle; all percents are based on the number of patients who had at least 1 dose in Cycle 1. b Patients who received 3 of 4 PS-341 doses within a cycle.

In the principal phase 2 study supporting this application, M34100-025, 202 patients with advanced, progressive multiple myeloma had been heavily pre-treated before entry on the study. All patients received VELCADE at the dose of 1.3 mg/m2 twice weekly for two weeks each 21 days. Drug exposure is detailed here and also discussed further in reference to summary statements at the end of the safety review section. The following table summarizes VELCADE exposure in study -025.

Table 30: Sponsor's Summary of Study Treatment by Cycle, Study M34100-025, (N=202)

	Treatment Cycle							
	1	2	3	4	5	6	7	8
	Number of patients [n (%)]:							
Treated with PS-341 in each cycle[a]	202 (100)	181 (90)	154 (76)	135 (67)	116 (57)	105 (52)	91 (45)	82 (41)
Completed each cycle[b]	190 (94)	161 (80)	136 (67)	119 (59)	99 (49)	93 (46)	78 (39)	75 (37)
At least 1 dose missed/held	41 (20)	54 (27)	49 (24)	50 (25)	43 (21)	32 (16)	24 (12)	18 (9)
At least 1 dose reduced	7 (3)	18 (9)	33 (16)	33 (16)	37 (18)	44 (22)	43 (21)	42 (21)
Last cycle in which PS-341 was received	21 (10)	46 (23)	25 (12)	36 (18)	11 (5)	17 (8)	7 (3)	39 (19)
Started dexamethasone in this cycle[c]	0	1 (<1)	20 (10)	6 (3)	29 (14)	5 (2)	14 (7)	3 (1)
Skipped a cycle	0	1 (<1)	3 (1)	0	2 (1)	1 (<1)	1 (<1)	0

a Patient received at least 1 PS-341 dose in the cycle; percents are based on the number of patients who had at least 1 dose in Cycle 1. b Patients who received ≥3 of 4 PS-341 doses within a cycle.
c A total of 78 patients added dexamethasone. (Source: sponsor's table 12-1, study report 025)

In this study, a total of 130 (64%) patients had at least 1 dose of PS-341 held for adverse events during the study. The most commonly reported events requiring doses to be held were thrombocytopenia (17%), neutropenia, neutropenia aggravated or decreased neutrophil count (14%), peripheral neuropathy NOS or peripheral neuropathy aggravated (8%), nausea (8%), and vomiting (7%) (see below). The first dose was held most commonly during Cycle 1 (36 patients) and Cycle 2 (34 patients). Furthermore, a total of 76 (38%) patients were reported on the adverse event and/or drug administration CRF to have had dose reductions implemented for adverse events. The most commonly reported events leading to dose reductions were peripheral neuropathy, including peripheral neuropathy aggravated (12%), fatigue or fatigue aggravated (6%), thrombocytopenia and nausea (4% each), and neutropenia or neutropenia aggravated and vomiting (3% each). Initial dose reduction most commonly occurred during Cycle 3 (22 patients), with a total of 38 patients requiring a dose reduction thereafter.

Twenty-nine percent (29%) of patients discontinued study drug because of an adverse event. Of these patients, most (53 of 58 patients) had not experienced a response to treatment on study. Overall, the most commonly reported adverse events leading to study drug discontinuation were peripheral neuropathy or peripheral neuropathy aggravated (4%), thrombocytopenia (4%), diarrhea and disease progression (3%), and dehydration and syncope (2%).

The mean total dose of PS-341 administered in this study to all 202 patients was 42.5 mg, with a range of 2.2 to 86.6 mg. The mean duration of treatment was 108 days (~4 months), with a range of 1 to 278 days (~9 months). The mean total VELCADE dose received was 80% of mean total dose expected to be administered based on number of actual cycles completed. Overall the average number of treatment cycles was 6, with 52% (105) patients receiving at least 1 dose in Cycle 6 and 41% (82) patients receiving at least dose of PS-341 in the last cycle (Cycle 8). The mean total number of PS-341 doses received was 19, with a range of 1 to 32 doses. The mean number of doses received was similar across treatment cycles, with the mean number of PS-341 doses received ranging from 3.4 to 3.7.

Evaluation of the mean total dose of PS-341 administered in each cycle revealed that, among patients who remained on treatment, the actual mean total PS-341 dose administered was ≥73% of expected dose in each treatment cycle. The maximum mean total PS-341 dose of 8.9 mg, which was 89% of the total mean PS-341 dose expected to be administered, was administered in Cycle 1. The mean total PS-341 dose administered decreased sequentially from Cycle 1 to Cycle 7; the minimum mean total PS-341 dose of 7.2 mg, which was 73% of the mean total PS-341 dose expected to be administered was administered in Cycle 7. It should be noted that the decrease in compliance was most likely related to PS-341 dose reductions, since the mean number of PS-341 doses administered in each treatment cycle was similar. The mean total PS-341 dose administered in Cycle 8 was 7.4 mg.

Combination treatment with dexamethasone was administered to a total of 78 patients. for these 78 patients, the mean total dose of dexamethasone administered in this study was 413 mg, with a range of 4 to 960 mg. No patient received dexamethasone in Cycle 1. A total of 1, 21, 25, 44, 42, 49, and 43 patients received dexamethasone in Cycles 2, 3, 4, 5, 6, 7, and 8, respectively.

Evaluation of the mean total dexamethasone dose administered in each cycle revealed that, among the patients who received such treatment, the actual mean total dose administered was ≥85% of the mean total dose expected. Only 1 patient incorrectly received dexamethasone in Cycle 2; this patient received a total of 160 mg, which was 100% of the dexamethasone dose expected to be administered. Across Cycles 3 to 8; the mean total dexamethasone dose administered ranged from 135 mg (Cycle 4) to 152 mg (Cycle 6).

The proportion of patients who missed at least 1 PS-341 dose within a cycle was similar in Cycles 1 through 6, with 20%, 27%, 24%, 25%, 21%, and 16% of patients missing at least one PS-341 dose in Cycles 1, 2, 3, 4, 5, and 6, respectively. The proportion of patients who missed at least 1 PS-341 dose in Cycles 7 and 8 was lower relative to Cycles 1 through 6, with 12% and 9% of patients missing at least 1 PS-341 dose in Cycles 7 and 8, respectively The proportion of patients requiring a PS-341 dose reduction increased over time on study, with 3%, 9%, 16%, 16%, 18%, 22%, 21%, and 21% of patients required PS-341 dose reductions in Cycles 1, 2, 3, 4, 5, 6, 7, and 8, respectively. Few patients missed an entire treatment cycle (i.e., missed all 4 PS-341 doses within a cycle, but resumed PS-341 in a subsequent cycle). Across all cycles, ≤1% of patients missed an entire treatment cycle during the study.

3 Methods and Specific Findings of Safety Review

The definition of the safety population is any patient receiving any amount of the study drug. Human toxicity information was acquired primarily through investigator reporting of adverse events in each of the clinical trials and supplemented by the pre-clinical experience. The sponsor's safety analysis included case report forms, tabulations, and summary tables of adverse events (AEs), severe adverse events, serious adverse events (SAEs), treatment-emergent adverse events, and drug-related treatment-emergent adverse events. Study datasets were constructed from case report forms (CRFs) using the Medical Dictionary for Regulatory Activities (MedDRA Version 4.0) to code the investigator's adverse event terms to preferred term and primary system organ class (SOC). Adverse effects were compared by study, exposure, and pre-existing patient conditions.

3.1. Clinical Safety Review:

The proposed indication for VELCADE is for adult patients with progressive MM after failure of two prior "front line" therapies for MM. VELCADE in phase II has been administered as a bolus IV injection of 1.0 or 1.3 mg/m^2/dose twice per week for 2 weeks (Days 1, 4, 8, and 11), followed by a 10 day rest period (cycle length 21 days). Patients received additional treatment cycles beginning 22 days after the first injection (day 1). A maximum of 8 treatment cycles was specified in the principal phase 2 clinical study. Although not discussed in this review, additional cycles were administered in an extension study (-029).

Three phase I (DM 98-104; LCCC9834/00-31; 98-104A) and two phase II (M34100-024 and M34100-025) study experiences were the primary datasets for this review of efficacy and safety for single agent VELCADE. Once weekly and twice weekly dosing were evaluated in patients with advanced solid tumors, hematological malignancies, and MM. Dose escalations in the phase

I studies ranged from 0.13 to 2.0 mg/m^2. The phase II trials in myeloma patients examined doses of 1.0 mg/m^2 and 1.3 mg/m^2 twice weekly. An additional phase I dose escalation study (M34100-027) was conducted to evaluate VELCADE in combination with gemcitabine in solid tumors. In this latter study, VELCADE was to be given twice weekly for four weeks of each six week cycle. Gemcitabine was given one hour after VELCADE on day 1 and day 8 of each three week cycle. This study is noted here because it is the principal source of the PK data for VELCADE to date.

Reviewer's comments: Traditionally, cytotoxic cancer chemotherapeutics are developed with dosing strategies that attempt to approach a maximum tolerated dosage (MTD) and a schedule of treatment that is defined empirically or on the basis of maximizing overall dose intensity. The sponsor selected the 1.3 mg/m^2 twice weekly schedule to evaluate DLT with correlative assessment of effects on the putative target of proteasome inhibition. Two confounding problems are associated with the patient population studied. Many patients had already received treatments potentially toxic to the nervous system, and the definition of "failure and progression following front line therapy" allowed for a great variety of treatments and coincident morbidities at baseline.

3.1.1 Clinical Pharmacology:

The metabolism and disposition kinetics of PS-341 was derived primarily from non-clinical studies in rats and monkeys. Only a small amount of human pharmacokinetic data exists. Single-dose kinetics have been obtained in solid tumor patients in phase I and in MM patients in phase II studies. The data developed for multiple-dose pharmacokinetics of PS-341 was derived from the phase I study in patients with solid tumors receiving PS-341 in combination with gemcitabine (M34100-027). A comprehensive characterization of the pharmacokinetics of PS-341 is lacking at this time.

After a single intravenous administration, plasma concentrations of PS-341 declined in a manner characterized by a rapid distribution phase followed by a longer terminal elimination phase. The rapid distribution period has a half-life of less than 10 minutes. Data from studies conducted in non-human primates have shown that the tissue distribution of PS-341 is extensive, with the exception of penetration into the central nervous system and various regions of the eye. In humans, the terminal elimination of PS-341 has an estimated half-life ranging from 5 to 15 hours. Exposure to PS-341 appears to be dose-dependent but not linear over the dose range of 1.45 to 2.0 mg/m^2. Dose-proportional increases were observed from 1.0 to 1.3 mg/m^2. In a group of solid tumor patients (n=17) the mean terminal elimination of PS-341 was 5.45 hours. The mean AUC 0-24 after the first dose (1.0 mg/m^2) of PS-341 was 30.1 hr*ng/mL. Following multiple doses of PS-341, a decrease in clearance was observed. A resulting increase in terminal elimination half-life and the AUC also occurs. Repeated dosing does not have an effect on the initial distribution kinetics of PS-341. No changes in estimated Cmax or the distribution half-life were observed were observed with repeated dosing at 72 hour intervals. However, in the solid tumor patients, the mean terminal elimination half-life increased from 5.45 to 19.7 hours, and the AUC (0-24) increased from 30.1 hr*ng/mL to 54.0 hr*ng/mL between the first dose to the third dose of the first Cycle (day 11). Similar findings have also been observed in nonclinical studies in rats and Cynomolgus monkeys.

Please see the Clinical Pharmacology and Biopharmaceutics review of this NDA for further information.

3.1.2 Phase I clinical trials experience:

Study DM98-194

Study DM98-194 was a single-center, phase 1, dose-escalation study designed to determine the DLT and the MTD of PS-341 administered as an IV bolus in 5-week treatment cycles and was the first clinical study of PS-341 initiated. In this study, PS-341 was administered once weekly for 4 consecutive weeks (on Days 1, 8, 15, and 22) followed by a 2-week rest period (14 days) after the last dose; one treatment cycle comprises this 5-week period. Patients with histologically confirmed advanced malignancies for which conventional therapy was unavailable were eligible for this study and 53 were enrolled. All patients were to receive at least 2 treatment cycles. After 2 treatment cycles, and every 2 cycles thereafter, measurable or evaluable disease parameters were documented. Patients with stable or responding disease were allowed to continue treatment indefinitely at the investigator's discretion. At least 2 patients were to be enrolled and treated at the initial PS-341 dose level, 0.13 mg/m^2, and monitored for toxicity. After all patients enrolled at a dose level completed 3 weeks of Cycle 1, enrollment at the next dose level could commence. Dose escalation and reduction was based on the analysis of all data using the continual reassessment method.

Dose selection (see also section VIII)

In murine and human xenograft tumor models, administration of PS-341 on a weekly regimen retained anti-tumor activity. Clinical dose selection was based on a preclinical study conducted in Cynomolgus monkeys in which PS-341 was administered at doses equivalent to 0.54, 0.80, and 1.20 mg/m^2 twice weekly for 4 weeks followed by a 2-week rest period. The MTD of PS-341 administered twice weekly for 4 weeks to Cynomolgus monkeys was 0.80 mg/m^2/dose. The starting dose of PS-341 selected for this clinical study, 0.13 mg/m^2, was 1/6 the MTD in Cynomolgus monkeys. Given the fact that the pharmacodynamics of PS-341 in humans was unknown at the time this study was initiated, a less intensive dose schedule was selected with PS-341 administration once weekly for 4 weeks followed by a 2-week rest period.

MTD definition

MTD was defined as the dose level having a mean posterior dose limiting toxicity probability closest to 25%. DLT was defined as any Grade 4 hematologic toxicity, any ≥Grade 3 nonhematologic toxicity with the exception of Grade 3 hyperbilirubinemia, or Grade 4 hyperbilirubinemia that occurred during the first treatment cycle and was considered related to study drug. The PS-341 doses (mg/m^2/dose) evaluated in this study were: 0.13, 0.25, 0.40, 0.60, 0.75, 0.80, 0.85, 0.90, 1.00, 1.10, 1.21, 1.32, 1.45, 1.60, 1.80, and 2.00.

Table 32 summarizes patient exposure to PS-341, overall and by dose level. The mean total dose of PS-341 administered in this study for all 53 patients was 22.7 mg (range: 1.0 to 89.6 mg) over a mean duration of treatment (i.e., from first dose to last dose of PS-341) of 76.8 days (range: 1 to 526 days). The mean number of PS-341 doses administered was 9.6 (range 1 to 57). The mean number of completed cycles was 2.2 (range 0 to 13).

Table 31: Exposure to PS-341, Overall and by Dose Level (Study 024, N = 53)

	PS-341 Dose (mg/m^2)							
Parameter	0.13-0.60 (n=10)	0.75-0.90 (n=9)	1.00-1.32 (n=8)	1.45 (n=6)	1.60 (n=13)	1.80 (n=2)	2.00 (n=5)	Total (n=53)
Total dose (mg)								
N	10	9	8	6	13	2	5	53
Mean (SD)	8.3 (14.3)	18.4 (16.2)	17.5 (11.2)	25.3 (21.1)	36.1 (12.9)	33.8 (14.1)	25.1 (13.6)	22.7 (18.2)
Median	2.3	15.2	15.6	23.4	36.5	33.8	27.6	19.8
Minimum, Maximum	1.0, 47.7	4.1, 55.7	7.2, 42.2	10.5, 42.7	5.6, 89.6	26.0, 41.6	4.2, 36.8	1.0, 89.6
Number of doses								
N	10	9	8	6	13	2	5	53
Mean (SD)	11.3 (16.3)	10.3 (9.2)	7.5 (4.0)	8.8 (4.5)	11.2 (7.1)	9.5 (2.1)	5.6 (2.9)	9.6 (8.9)
Median	6.0	8.0	7.5	8.0	11.0	9.5	6.0	8.0
Minimum, Maximum	4, 57	2, 32	4, 16	4, 16	2, 28	8, 11	1, 8	1, 57
Duration of treatment (days)[a]								
N	10	9	8	6	13	2	5	53
Mean (SD)	91.9 (154.8)	80.6 (81.9)	55.1 (39.5)	66.3 (40.9)	94.6 (68.6)	79.5 (29.0)	39.2 (23.2)	76.8 (83.9)
Median	39.0	56.0	53.0	56.5	86.0	79.5	43.0	56.0
Minimum, Maximum	22, 526	8, 272	22, 141	22, 135	8, 233	59, 100	1, 58	1, 526
Number of completed cycles[b]								
N	10	9	8	6	13	2	5	53
Mean (SD)	2.7 (3.68)	2.4 (2.40)	1.8 (1.04)	2.2 (1.17)	2.5 (1.85)	2.0 (0.00)	1.2 (0.84)	2.2 (2.2)
Median	1.5	2.0	1.5	2.0	2.0	2.0	1.0	2.0
Minimum, Maximum	1, 13	0, 8	1, 4	1, 4	0, 7	2, 2	0, 2	0, 13

Sponsor's table 14.3.1 protocol DM98-194

Thirty-one (58%) of 53 patients received at least 2 complete treatment cycles (4 of 4 PS-341 doses once weekly in both Cycles 1 and 2). (Note: 2 patients discontinued during the rest period after 2 treatment cycles; therefore 29 patients were considered to have completed the protocol). The proportion of patients who completed at least 2 treatment cycles was lowest at the highest dose level of 2.00 mg/m^2 dose level (40%). More than 65% of patients in each of the 1.45, 1.60, and 1.80 mg/m^2 dose groups completed 2 or more treatment cycles; in the 3 lowest dose levels 50% to 56% of patients completed 2 or more treatment cycles.

Seventeen (32%) of 53 patients continued treatment beyond Cycle 2. The highest proportion of patients within each dose level who continued treatment beyond 2 cycles was at the 1.60 mg/m^2 dose level, with 7 (54%) of 13 patients at this dose level receiving more than 2 cycles of PS-341. This is compared to 2 (20%) of 10 patients at the 0.13-0.60 mg/m^2 dose level, 3 (33%) of 9 at the 0.75-0.90 mg/m^2 dose level, 2 (25%) of 8 at the 1.00-1.32 mg/m^2 dose level, 2 (33%) of 6 at the 1.45 mg/m^2 dose level, 1 (50%) of 2 at the 1.80 mg/m^2 dose level, and 0 (0%) of 5 patients at the 2.00 mg/m^2 dose level.

The next 2 sponsor's tables below show the treatment-emergent adverse events by dose level and the drug-related treatment-emergent adverse events of grade 3 or 4 severity. The most frequently reported adverse event category was GI.

Table 32 Sponsor's Treatment-Emergent Adverse Effects by Dose Level

	n (%)	Events	PS-341 Dose Levels (mg/m²)						
Parameter	N=53	N= 54	13 - .60 N=10	.75 - .90 N=9	1.00 - 1.32 N=8	1.45 N=6	1.6 N=13	1.8 N=2	2.0 N=5
Any Adverse Event	21 (40)	54 (100)	5 (50)	2 (22)	2 (25)	2 (33)	8 (62)	0	2 (40)
Gastrointestinal disorders	6 (11)	11(20)	1 (10)	0	0	1 (17)	3 (23)	0	1 (20)
Diarrhea NOS	5 (9)	5 (9)	0	0	0	1 (17)	3 (23)	0	1 (20)
Vomiting NOS	2 (4)	2 (4)	1 (10)	0	0	1 (17)	0	0	0
Abdominal pain NOS	1 (2)	4 (7)	0	0	0	0	1 (8)	0	0
General disorders and administration site conditions	5 (9)	9 (17)	2 (20)	1 (11)	0	0	2 (15)	0	0
Pyrexia	5 (9)	6 (11)	2 (20)	1 (11)	0	0	2 (15)	0	0
Application site pain	1 (2)	2 (4)	0	0	0	0	1 (8)	0	0
Rigors	1 (2)	1 (2)	0	0	0	0	1 (8)	0	0
Musculoskeletal and connective tissue disorders	5 (9)	7 (13)	1 (10)	0	1 (13)	0	2 (15)	0	1 (20)
Back pain	3 (6)	3 (6)	1 (10)	0	1 (13)	0	0	0	1 (20)
Pain in limb	2 (4)	3 (6)	0	0	0	0	2 (15)	0	0
Arthralgia	1 (2)	1 (2)	0	0	0	0	1 (8)	0	0
Renal and urinary disorders	5 (9)	7 (13)	1 (10)	1 (11)	1 (13)	1 (17)	1 (8)	0	0
Bilateral hydronephrosis	1 (2)	1 (2)	1 (10)	0	0	0	0	0	0
Bladder spasm	1 (2)	1 (2)	0	0	1 (13)	0	0	0	0
Hematuria	1 (2)	1 (2)	0	0	1 (13)	0	0	0	0
Renal failure NOS	1 (2)	1 (2)	1 (10)	0	0	0	0	0	0
Renal impairment NOS	1 (2)	1 (2)	0	1 (11)	0	0	0	0	0
Ureteral disorder NOS	1 (2)	1 (2)	0	0	0	0	1 (8)	0	0
Urinary retention	1 (2)	1 (2)	0	0	0	1 (17)	0	0	0
Vascular disorders	5 (9)	5 (9)	1 (10)	0	0	0	3 (23)	0	1 (20)
Hypotension NOS	2 (4)	2 (4)	0	0	0	0	2 (15)	0	0
Cerebrovascular accident NOS	1 (2)	1 (2)	0	0	0	0	1 (8)	0	0
Deep venous thrombosis NOS	1 (2)	1 (2)	1 (10)	0	0	0	0*	0	0
Orthostatic hypotension	1 (2)	1 (2)	0	0	0	0	0	0	1 (20)
Cardiac disorders	2 (4)	2 (4)	0	0	0	0	2 (15)	0	0

Source: Millennium Pharmaceuticals, Inc. Protocol No.: DM98-194 TABLE 14.3.1.9

Table 33: Drug-Related Treatment-Emergent Adverse Events of Grade 3 or 4 Severity Overall and by Dose Levels

				PS-341 Dose Levels (mg/m²)						
Parameter	Statistic	Patients N=53	Events N=19	.13 - .60 N=10	.75-90 N=9	1.00 - 1.32 N=8	1.45 N=6	1.6 N=13	1.8 N=2	2.0 N=5
Any Drug-Related Grade 3 or 4 Adverse Events	n (%)	14 (26)	19 (100)	1 (10)	0	1 (13)	1 (17)	7 (54)	1 (50)	3 (60)
Gastrointestinal disorders	n (%)	8 (15)	8 (42)	0	0	0	0	5 (38)	1 (50)	2 (40)
Diarrhea NOS	n (%)	7 (13)	7 (37)	0	0	0	0	4 (31)	1 (50)	2 (40)
Gastro-esophageal reflux disease	n (%)	1 (2)	1 (5)	0	0	0	0	1 (8)	0	0
Nervous system disorders	n (%)	3 (6)	3 (16)	0	0	0	1 (17)	0	0	2 (40)
Dysesthesia NEC	n (%)	1 (2)	1 (5)	0	0	0	0	0	0	1 (20)
Peripheral sensory neuropathy	n (%)	1 (2)	1 (5)	0	0	0	1 (17)	0	0	0
Syncope	n (%)	1 (2)	1 (5)	0	0	0	0	0	0	1 (20)
Vascular disorders	n (%)	2 (4)	2 (11)	0	0	0	0	1 (8)	0	1 (20)
Hypotension NOS	n (%)	1 (2)	1 (5)	0	0	0	0	1 (8)	0	0
Orthostatic hypotension	n (%)	1 (2)	1 (5)	0	0	0	0	0	0	1 (20)
Cardiac disorders	n (%)	1 (2)	1 (5)	0	0	0	0	1 (8)	0	0
Tachycardia NOS	n (%)	1 (2)	1 (5)	0	0	0	0	1 (8)	0	0
Eye disorders	n (%)	1 (2)	1 (5)	0	0	0	0	1 (8)	0	0
Vision abnormal NOS	n (%)	1 (2)	1 (5)	0	0	0	0	1 (8)	0	0
General disorders and administration site conditions	n (%)	1 (2)	2 (11)	1 (10)	0	0	0	0		
Fatigue	n (%)	1 (2)	1 (5)	1 (10)	0	0	0	0		
Performance status decreased	n (%)	1 (2)	1 (5)	1 (10)	0	0	0	0		
Investigations	n (%)	1 (2)	1 (5)	0	0	1 (13)	0	0		
Weight decreased	n (%)	1 (2)	1 (5)	0	0	1 (13)	0	0		

Note: Events with missing Relation to PS341 are included in the analysis.
Events with missing severity are set to Severe for the analysis.

Source: Millennium Pharmaceuticals, Inc. Protocol No.: DM98-194 TABLE 14.3.1.5

Summary of Safety Findings for DM98-194:

The maximally tolerated dose of PS-341 when administered once a week for 4 weeks (on Days 1, 8, 15 and 22) followed by a 13-day rest period was determined to be 1.60 mg/m2. Dose limiting toxicities experienced in this study included tachycardia and hypotension, abnormal vision, and diarrhea in 3 patients at the 1.60 mg/m2 dose level; diarrhea in 1 patient at the 1.80 mg/m2 dose level; and diarrhea, syncope and orthostatic hypotension, and intermittent diarrhea in 2 patients at the 2.00 mg/m2 dose level.